

TIVA TRAINER: PHARMACOKINETIC SIMULATION

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Tivatrainier© is a pharmacokinetic simulation program, written for teaching intravenous anesthesia and explaining the concepts of pharmacokinetics, opioid-propofol interaction, Target Controlled Infusion and Effect Target Controlled Infusion. It can be downloaded from <http://www.eurosiva.org> and be used freely for a limited number of times. The contents of the workshop will be dependent on the requirements of the participants. If you are planning to participate in the workshop you are invited to write down any question you have on intravenous anaesthesia or the use of Tivatrainier. The questions will be collected at the beginning of the workshop and we will try to answer them during the workshop. An audience response system will be used during the workshop.



INFUSION PUMPS AND PHARMACOKINETIC MODELS

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The workshop will be run in an informal manner, to encourage interaction between delegates and the workshop leaders, and to allow delegates to develop “hands-on” familiarity with current infusion pumps. Topics to be covered will depend strongly on the experience and interests of delegates.

Potential topics include:

1. “Hands-on” experience with set-up and running a TCI system
2. Practical aspects of TIVA and TCI
3. Principles of pharmacokinetics

4. Principles of target-controlled infusion (TCI)
5. Brief history of the development of the TCI concept
6. Brief history of the development of TCI systems
7. TCI opioids
8. Pharmacokinetic interactions
9. Pharmacodynamic interactions
10. Accuracy of TCI systems
11. Effect-site targeted TCI
12. Comparisons of available models for commonly used drugs
13. Special patients groups (i.e. elderly, obese ...)

NEUROMONITORING WORKSHOP

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Unfortunately, here is no “Gold Standard Measure” of anaesthetic depth, so indirect (surrogate) parameters must be used. These parameters are mainly based on either the spontaneous or the evoked electroencephalogram. Various devices have been introduced and their performance in improving anaesthetic titration have been evaluated. The essence of the available literature and practical experience so far can be characterized as follows:

- Depth of anaesthesia monitors may contribute to a further improvement and increasing predictability to titrate anaesthesia
- The overall clinical utility is limited by confounding factors influencing the performance
- Drug interactions as used in anaesthesia practice are often less well described by EEG-based monitors
- Clinical relevance of differences between specific monitors remain to be demonstrated

It has to be pointed out that all EE-derived parameters will always quantify the degree of cortical activity/suppression, regardless of the underlying level of consciousness. The potential of depth of anaesthesia monitors to detect and subsequently avoid memory formation and recall is likely but still more evidence is required.

This workshop is designed to discuss the latest development in brain function monitoring and its implication on conducting intravenous anaesthesia. The workshop aims to explain the basic technology of

EEG-derived parameters as well as their advantages and limitations when applied in clinical anaesthesia. Practice advice is given by demonstrating video-based case scenarios along with explanatory slides. Delegates will be given the opportunity to present and discuss their own experience with neuromonitoring and are encouraged to bring along case material.

HUMAN PATIENT SIMULATOR: TIVA TCI CASE REPORTS

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Clinical simulation is becoming more and more important in the education of medical students and in the continuous qualification, becoming or being an anaesthesiologist.

Also patient safety issues cannot be experienced in the patients themselves, but have to be trained in a simulated set.

Tiva and TCI infusion mode cannot be simulated easily, because it is necessary that many different devices (monitors for depth of anaesthesia and hemodynamic, different pumps, computers) talk to each other and react to the delivery of drugs.

We present a human patient simulator connected to Tiva-TCI pumps and BIS monitor.

We have developed the necessary models to simulate the correct responses to the administration of different amount of the most commonly used drugs for Tiva-TCI, allowing hands-on practice in three different cases: a young healthy male, an old fat female and an old man ASA 3.

The participants can experience the proper target of the drugs used, and discover, without any risk for any patient, the meaning of TCI compared to continuous infusion, and how to react to eventual side effects of the procedure.

The workshop also gives an example of how simulation training can be integrated into a curriculum for the training of Tiva-TCI.

The human pharmacodynamic variability is strictly connected to the risk of over- or under-dosage of the drugs, used by the anaesthesiologist, and the simulation system has the capability to reproduce the clinical situations to a high degree of realism.

THE HISTORY AND EVOLUTION OF INTRAVENOUS ANAESTHESIA

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"The farther backward you can look, the farther forward you are likely to see."

Sir Winston Churchill

Our current 'state of the art' stands on the shoulders of early pioneers; William Harvey (circulation, 1628), Christopher Wren (i.v. wine & ale in dogs with bladder and quill, 1657), Johann Elsholtz (extractum opii in dogs, pointed metal syringe, 1667), Frances Rynd (s.c. morphine in creosote with a hollow needle in patients, 1844), Charles Pravaz (metal syringe, 1853), Alexander Wood (injected morphine with syringe, 1853), Pierre-Cyprien Ore (i.v. chloral hydrate, 1872), Karwkwow & Fedoroff (i.v. hedonal, 1909), Noel & Souttar (i.v. paraldehyde, 1913), Peck & Meltzer (i.v. magnesium sulphate, 1916), Naragawa (i.v. ethyl alcohol, 1921), Cardot & Laugier (i.v. ethyl alcohol, 1922). Important barbiturate milestones; synthesis of the first barbiturate acid derivative with hypnotic activity (Fisher & von Mering, 1903), Somifen was a mix of the first two barbiturates used for intravenous anaesthesia (Bardet, 1921); Pernosten was the first barbiturate to regain widespread use intravenous use (1927), hexobarbitone was the first short-acting barbiturate with rapid onset of action and widespread popularity (Weese & Scharpf, 1932), thiopentone begins clinical trials (Lundy & Waters, 1934), first clinical use (1936), "an ideal method for euthanasia" (Pearl Harbour, 1941). Opium used to relieve pain (Theophrastus, 3rd century BC). Friedrich Wilhelm Sertürner described the active ingredient, which he called 'morphicum' (1806). Schneiderlein described an anaesthetic technique using 70mg morphine with scopolamine (1900). Morphine derivatives; papaveretum (1901), hydrocodone bitartrate (1923). Pethidine was the first synthetic opioid (1923). Fentanyl synthesized by Paul Janssen (1960). Lowenstein used large doses of morphine (0.5 to 3 mg/kg) and relaxant for cardiac surgery (1965). Fentanyl anaesthesia first described by Grell (1970). Stanley used high dose fentanyl (75 mcg/kg) for cardiac surgery (1979). 1970s; sufentanil and carfentanil, 1980s; alfentanil, 1990s; remifentanil. Benzodiazepines were discovered by Sternbach, working for Hoffman La Roche in New Jersey. In 1957 the original compound was found to have hypnotic, anxiolytic and muscle relaxant effects and the first benzodiazepine, chlordiazepoxide (Librium) was launched in the UK in 1960, followed by diazepam (Valium) in 1963. By 1983 there were 17 benzodiazepines in the market. By the late 1970s benzodiazepines had become the most commonly

prescribed of all drugs in the world. In 1960, Janssen developed a group of butyrophenones (haloperidol and droperidol). The combination of a butyrophenone and an opioid was used by De Castro and Mundeleer (1959), this later became known as 'neuroleptanaesthesia.' Ketamine (1962). First clinical trials of propofol (Kay & Rolly, 1977). In 1942, James Dutcher and Oskar Wintersteiner, working with Richard Gill's supplies (from the plants used by the Indians in Ecuador), established with certainty that the origin of the d-tubocurarine chloride (previously isolated by King) was *Chondodendron tomentosum*. The idea to use curare in anaesthesia originated with Lewis H Wright in 1940, after he watched film on the use of Intocostrin in shock therapy. The introduction of curare into anaesthetic practice changed the basic philosophy of anaesthesia, and seemed to stimulate the organization of the speciality. Succinylcholine (1952). Physostigmine, an alkaloid isolated from the calabar bean (or esere nut, an ordeal poison) extracted (1863). Neostigmine (1931). A new concept in reversal; chemical encapsulation of rocuronium by a cyclodextrin derivative (2005). Where would we be without the humble disposable syringe? Patented (Arthur E. Smith, 1949-50, Colin Murdoch, 1956), Becton, Dickinson & Co. created the first mass-produced disposable glass syringe and needle (1954), Roehr Products introduced a plastic disposable syringe called the Monoject (1955), Becton Dickinson introduced its first plastic disposable syringe called the Plastipak. History of pharmacokinetics; calculations related to ether (Buchanan, 1847), enzyme kinetics (Michaelis & Menten, 1913), the one-compartment open model with bolus intravenous injection and constant rate intravenous infusion equations (Widmark and Tandberg, 1924), uptake, distribution and elimination of diethyl ether (Haggard, 1924), renal clearance concept (Moller, 1929), intravascular transport of a dye indicator (Jolliffe & Smith, 1931); mean transit time (Hamilton, 1931), zero order elimination (Widmark, 1932), volume of distribution and rate of absorption defined (Dominguez, 1934), pharmacokinetics really gets underway with a five-compartment physiologically based pharmacokinetic model (Teorell, 1937), bioavailability (Oser, 1945), equations specifying the intravenous infusion rate profile required to achieve and maintain a constant specified plasma concentration of a drug whose pharmacokinetics could be described by a linear multicompartment model (Kruger-Theimer, 1968), effect site (Sheiner & Stanski, 1979, Hull, 1979). Other more recent developments; context-sensitive half time, relevant decrement time, mean effect time, front-end pharmacokinetics, t_{peak} concept, isobolograms, response surface modelling, population pharmacokinetic modelling and covariate analysis. In 1981, Schwilden suggested and demonstrated the use of computer controlled infusion pumps to implement exponentially declining infusion schemes. The first

drugs administered in this way were etomidate and alfentanil. Later infusion schemes and were modified and infusion rate control algorithms were developed to allow the anaesthetist to vary the plasma target concentration as required. The use of a prototype TCI system was first described in 1988 by Schuttler et al. This was followed by a system developed by the University of Glasgow by Gavin Kenny (1990) based on an external computer connected to a volumetric pump. Early research systems were described as CATIA (computer assisted total intravenous anaesthesia), TIAC (titration of intravenous anaesthetics by computer), CACI (computer assisted continuous infusion) and CCIP (computer controlled infusion pump). The launch of 'Diprifusor' as the first commercially available TCI system for propofol in 1996 was the cornerstone of a successful research period within the last decade, which evaluated the pharmacokinetic foundations of computer assisted intravenous drug delivery. In 1997, the term "target controlled infusion" (TCI) was proposed as a general term to embrace the earlier descriptors. New TCI systems offering greater functionality than the Diprifusor pumps are now entering the market. Cardinal Health (Alaris Asena PK pump) and Fresenius Kabi (Orchestra system) offer "open" TCI (these pumps do not require the use of tagged pre-filled syringes, which tie the user to a specific brand of drug). We are now in a period where effect-site TCI administered remifentanyl/alfentanil/sufentanil and propofol are part of the routine anaesthetic techniques. and many more advances ...monitoring depth of anaesthesia; brainstem auditory evoked potentials, bispectral index, entropy research into closed loop control.

A more complete handout is available at URL:

<http://pkpdttools.com/downloads/pdf/history.pdf>

TIVA AND THE ANESTHETIC PIPELINE: THE NEW DRUGS IN DEVELOPMENT THAT MAY RADICALLY ALTER TOTAL INTRAVENOUS ANESTHESIA

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The next 10 years will see the introduction of novel propofol formulations, hypnotics, muscle relaxants, and analgesics. These will all profoundly affect how we administer drugs by total intravenous anaesthesia.

The primary goal for novel propofol formulations is to alter or completely remove the lipid. Since propofol is almost totally insoluble in water, one approach is to solubilize propofol in cyclodextrins rather than lipids. Cyclodextrins are water-soluble cyclic carbohydrates

with a hydrophobic cavity that can accommodate a lipid-soluble drug molecule. A cyclodextrin formulation, "Captisol-Enabled Propofol" is presently in development by CyDex (a company that probably didn't realize that Cidex is also the trade name for glutaraldehyde, a highly toxic, colorless disinfectant). Another clear formulation of propofol, Cleofol, has recently been introduced in India by Themis Medicare. This appears to be a micellular formulation. It will radically alter total intravenous anesthesia partly by the damage it does to infusion sets. It is also associated with an 89% incidence of severe pain on injection and venous phlebitis. However, it is recommended for patients who require a strictly vegetarian anesthetic.

MGI Pharmaceuticals is pursuing development of water-soluble phosphate-linked propofol prodrug, "Aquavan". On ester hydrolysis Aquavan releases phosphate and formaldehyde. Aquavan has a significantly slower onset when compared with propofol because the drug must undergo ester hydrolysis to release the active moiety. Peak effect occurs nearly 8 minutes after bolus injection. Many subjects receiving Aquavan report a paresthesia on injection, which has been described as "a transient unpleasant sensation of burning or tingling of moderate severity in the anal and genital region." This is similar to the genital and rectal discomfort associated with phosphenytoin and dexamethasone, and probably reflects the effect of phosphate liberation, which is also released by hydrolysis of phosphenytoin and dexamethasone.

Astra Zeneca is currently beginning development of a new hypnotic with remarkable pharmacokinetic properties. Originally developed by Theravance, this compound (TD-4756) has pharmacokinetic properties very similar to remifentanyl. A hypnotic with ultra-rapid metabolism could revolutionize anesthetic practice over the next 20 years as much as Diprivan did two decades ago.

There are exciting developments in the area of opioid pharmacology as well. However, the most exciting development is not directed towards new opioids, but towards drugs that permit one to manage opioid toxicity. BIMU8 is a 5-HT₄ (a) agonist being investigated by Novartis. BIMU8 selectively reverses fentanyl-induced ventilatory depression in rats without affecting the analgesic response. Methylnaltrexone is a peripherally acting opioid antagonist being developed by Wyeth. BIMU8 and methylnaltrexone open the possibility that we may be able to deliver opioids and achieve systemic analgesia, without the dose-limiting side effects of ventilatory depression, ileus, pruritis, nausea, and vomiting. If that was the case, target controlled delivery of opioids, 5-HT₄ (a) agonists, and methylnaltrexone could open entirely new avenues for profound

post-operative analgesia without incurring the risks of opioid toxicity.

STRATEGIES TO REDUCE PATIENT HARM FROM TIVA

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Emerging information technologies, such as decision support systems, computer based patient records, and TIVA based care do not merely afford the possibility of enhanced performance but participate in an "intellectual partnership." In this partnership, the human being and the computer are viewed as dynamically interacting, resulting in distributed performance. This interaction can be understood in terms of learning, involving the division of labor and the development of a subtle interdependence over time.

TIVA based practice offers great promise but also several potential dangers and unintended consequences. In considering the impact of this partnership, we can distinguish between "effects with" and "effects of" the technology. Effects with refers to changes in intellectual performance while people learn and interact with technologies, whereas effects of refers to enduring changes resulting from human interaction with technology, even when people are away from machines. The enduring effects can result in significant changes in performance.

Numerous cognitive and social challenges are involved in understanding and engineering an effective use of emerging technology in the workplace. In recent years, cognitive science research has made progress in understanding learning processes and skill acquisition in complex technology-based domains. Advances in the use of information technology are rapidly changing the way we think, reason, make decisions, and interact with others. Beyond merely extending human memory, these artifacts or tools affect human reasoning in ways that may be subtle, yet profound.

Issues related to the complex interaction among health care workers and emerging information technologies are rapidly coming to the fore in the field of medical informatics. As cognitive artifacts, such systems have the potential to greatly enhance and extend human capabilities by providing health care workers with access to the latest information and assistance in performing complex cognitive tasks, including medical diagnosis, treatment planning and management of complete anesthetic plans.

Although considerable effort has been expended in the development of these technologies, far less work has been devoted to examining their effects on the basic cognitive processes involved in health care. The effects of systems on complex decision processes and human knowledge organization remain to be more fully explored.

TIVA in the learning environment seeks to bring information and expertise to the bedside, with the goal of reducing reliance on memory and reduce hand-written computation and documentation with its problems of legibility and reliability. At the same time, presentation of information in rigid categories, a common attribute of computerized data entry, storage and retrieval systems may alter the cognitive processes of physicians, especially learners whose approach to information gathering and processes is still developing. Studies have shown that information gathering and decision making is changed when the source of information changes from a paper-based record (with a narrative structure) to an electronic computerized storage mode (with an underlying relational database).

Evidence is emerging that computerized presentation and manipulation of information may alter human cognitive and decision processes in unexpected and unintended ways. Reducing the unintended harm from TIVA requires guidance from expert human factors scientists guided by active engagement of clinicians in the design and application of TIVA. A key challenge remains how to incorporate technology into the local learning environment and culture in ways that optimize its implementation and use, and maximize the benefits for learning and patient care.

BEYOND THE STEADY STATE

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Donald A. Schön (1973) wrote the following in his book entitled 'Beyond the Stable State'. Pages 28-9.

The loss of the stable state means that our society and all of its institutions are in continuous processes of transformation. We cannot expect new stable states that will endure for our own lifetimes.

We must learn to understand, guide, influence and manage these transformations. We must make the capacity for undertaking them integral to ourselves and to our institutions.

We must, in other words, become adept at learning. We must become able not only to transform our institutions,

in response to changing situations and requirements; we must invent and develop institutions which are 'learning systems', that is to say, systems capable of bringing about their own continuing transformation.

The task which the loss of the stable state makes imperative, for the person, for our institutions, for our society as a whole, is to learn about learning.

What is the nature of the process by which organizations, institutions and societies transform themselves?

What are the characteristics of effective learning systems?

What are the forms and limits of knowledge that can operate within processes of social learning?

What demands are made on a person who engages in this kind of learning?

The title of this talk is a 'pharmacokinetic adaptation' of the title of Schön's book. Many anaesthetists today have been trained to use an intravenous induction technique, followed by maintenance with nitrous oxide and volatile anaesthetic agents. They are excellent and skilled anaesthetists. They practice in a steady state. As much as they might like to learn a new technique, such as effect-site controlled propofol and remifentanyl target controlled infusions, guided by an electroencephalographic measure of drug effect, taking the first step is difficult. What motivates a professional to want to change from one technique (in which they are an expert) to another (in which they are a novice)? What are the obstacles facing a professional who wants to change?

I will share some anecdotes of my own transition from one steady state (volatile based anaesthesia) to another (effect-site TCI based anaesthesia) over the past ten years. Hopefully, we will manage to have a highly interactive (and entertaining) session.

A more complete handout is available at URL:

<http://pkpdttools.com/downloads/pdf/beyondss.pdf>

THE ROLE OF REMIFENTANIL ON THE ICU

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Untreated pain, which has been shown to be common on ICU, is associated with an increased duration of mechanical ventilation, and an increased risk of post-traumatic stress disorder. Traditional sedative regimens are commonly benzodiazepine-based, with ad hoc analgesic therapy. Since the opioids provide

analgesia in addition to anxiolysis, sedation, tube tolerance and suppression of airway reflexes, there is a strong argument in favour of opioid-based sedation. The pharmacokinetic characteristics of morphine and fentanyl are not optimal. After an hour fentanyl infusions result in accumulation and a dramatic increase in context-sensitive half-time (CSHT). While the increase in the CSHT of morphine is less dramatic, it possesses active metabolites prolong the clinical effects.

The pharmacokinetics of remifentanyl are ideal for use by infusion. Equilibration between compartments is rapid, facilitating rational titration of the infusion rate. Metabolism by non-specific esterases present throughout the body is rapid, context-insensitive, and unaffected by renal or hepatic impairment.

Compared with benzodiazepine-based regimens, remifentanyl-based regimens produce significant benefits including decreased duration of mechanical ventilation, decreased duration of ICU stay, and greater ease of control of awakening for repeated neurological assessments. A pharmaco-economic analysis showed that the greater costs of remifentanyl were offset by the shorter duration of ventilation and ICU stay. A study comparing remifentanyl- with fentanyl-based sedation found similar safety, efficacy and extubation times. For ethical and practical reasons, it may be some time before the clinically apparent benefits of remifentanyl are demonstrated in a rigorous scientific manner.

KETAMINE: A NEW OLD DRUG

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Pain is a predictable part of the postoperative time, besides an increased focus on pain management acute pain after surgery is an usual experience for surgical patients (Approximately 80%). Side effect arising from ineffective postoperative pain management include, but are not limited to, deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia, and depression. Therefore, there is the need to optimise perioperative pain management. During the last several years the effects of noxious stimulation on nervous system function and our knowledge of pain processing have increased substantially. Severe poorly controlled noxious stimulation initiates changes in both peripheral and central nervous system that lead to amplification and persistence of pain. There is a substantial amount of evidence that N-methyl-d-aspartate (NMDA) receptors play a main role in the development and maintenance of central hyperactive states underlying the behavioural

manifestations of pain facilitation such as hyperalgesia, allodynia, and spontaneous pain. The main reason of renewed interest on the use of ketamine is its action as noncompetitive NMDA-antagonist. Ketamine is a phencyclidine derivative developed in the 1960's as a general anaesthetic, it has been pointed out that subanesthetic dose of the drug can prevent the induction of central sensitization caused by stimulation of peripheral nociception as well as blocking the wind-up phenomenon. A subanesthetic dose of ketamine is defined as a bolus dose of <1 mg/kg and an infusion rate of <20 mg/kg/min (1.2 mg/kg/h). It has also been reported that receptor activation by opioids leads to a sustained increase in glutamate synaptic effectiveness at the level of NMDA receptors. Opioids when used alone in large doses for a prolonged period induce tolerance, which may lead to increased postoperative pain. Ketamine, by blocking these NMDA receptors, can prevent the development of tolerance. The timing of ketamine administration is a crucial component in pain prevention. Several authors have compared the effects of ketamine administration before surgery with those of one ketamine administration at the end of surgery to test its "preemptive" analgesic properties. However, nociceptive signals are generated throughout surgery. A single injection of a short-acting drug such as ketamine either before or after incision will not provide an analgesia that lasts far into the postoperative period. To prevent pathologic and postoperative pain, ketamine needs to be applied at least throughout the operation and likely for a period of time into the postoperative phase. Thus, the idea of "preemptive" analgesia has changed into "periemptive" analgesia. Another reason for the renewed interest in ketamine is the availability of S(+) ketamine. Ketamine has a chiral center at the carbon-2 atom of the cyclohexanone ring, and therefore exists as the optical stereoisomers S(+) and R(-) ketamine. Until recently, ketamine was marketed as a racemate, containing equimolar amounts of the enantiomers. In some European countries S(+) ketamine has recently been approved for clinical use. S(+) ketamine, formulation of the drugs that contains S(+) pure stereoisomers, has a fourfold greater affinity for NMDA receptors than does R(-) ketamine. This difference results in a clinical analgesic potency of S(+) ketamine approximately two times greater than the racemic one and four times greater than R(-) ketamine, whereas S(+) ketamine has a shorter duration of action. Moreover, some authors have pointed out that S(+) induced less decline in intellectual capacities than racemic ketamine at equianalgesic effects. In conclusion, Ketamine in subanaesthetic dose has been shown to be effective in reducing post operative pain and should be considered as an additive in the surgical population with large opioid requirements. Presently, there are insufficient evidences to show a clear benefit of S(+) ketamine as compared with racemic ketamine. Future

clinical trials should focus on the influence of small ketamine dose used for acute postoperative pain on long-term pain syndromes (postmastectomy, thoracotomy).

References:

- 1) Bell RF, Dahl JB, Moore RA, Kalso E Perioperative ketamine for acute postoperative pain (Review) Cochrane Database Syst Rev. 2006 Jan 25;(1)
- 2) De Kock M. F., Lavand'homme P.M. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain Best Practice & Research Clinical Anaesthesiology Vol. 21, No. 1, pp. 85e98, 2007
- 3) Vadivelu N., Sinatra R. Recent advances in elucidating pain mechanisms. Current Opinion in Anaesthesiology 2005, 18:540–547

NSAIDS AND COX

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The first report of willow bark was published in England by Reverend Edward Stone in 1763, although such preparations date back over thousands of years. The active component of willow bark was later identified as salicin, which is metabolized to salicylate. The Bayer pharmaceutical company produced the commercial preparation “aspirin” (they also made “heroin”) and by 1950 it was in the Guinness Book of Records as the world's best-selling painkiller. Other drugs with similar clinical effects were soon developed (Non-Steroidal Anti-Inflammatory Drugs). In 1982 Professor Sir John Vane Sune Bergström and Bengt Samuelsson won the Nobel Prize for discovering the role of aspirin in inhibiting prostaglandin production and in 1992 the cyclooxygenase isoenzymes (COX 1 and 2) were cloned [1,2].

Tissue injury, acute and chronic peripheral inflammation, interleukins and spinal cord injury increase the expression of COX-2 and releases neurotransmitters, including substance P (SP) and glutamate, and results in increased local concentrations of arachidonic acid metabolites (prostaglandins and leukotrienes). These agents directly activate C pain fibres, degranulate mast cells (releasing histamine and cytokines), or lead to plasma extravasation and oedema. Prostaglandins (PG) increase the sensitivity of nociceptive transduction mechanisms and enhance elicitation and synaptic transfer of pain signals in the spinal cord increasing the response to painful stimuli (hyperalgesia). Direct administration of PGs to the spinal cord causes hyperalgesia and allodynia. Administration of cyclooxygenase inhibitors reduces the

development of hyperalgesia and allodynia [3] and I believe there is a role for COX-2 inhibition in blocking the synthesis of prostaglandins in the early phase of inflammation. With the early administration of a COX-2 inhibitor, peripheral and central sensitisation could be significantly reduced, potentially being reflected in improved anti-nociception. The time when this secondary injury starts and ends is unknown. We can only be sure that it will extend into the post-operative period. A number of studies have used stress response chemical markers in an attempt to determine the onset and duration of early inflammation in different surgeries. The levels of these markers give an indication of the duration and severity of the inflammatory response. Interleukin 6 is one of the most reliable and important markers (Shenkin A et al 1989). It is a multifunctional protein, released early during surgery, which mediates the release of acute-phase proteins and causes inflammation. In one study, interleukin 6 increased and achieved a peak at around four hours after skin incision. It then decreased, returning to normal 72 hours after surgery [4]. Hence we may assume that the inflammatory response starts immediately after tissue injury and peaks four hours after skin incision. There is also evidence that this can occur even if somatic sensation is blocked with local anaesthesia [5]. Any anti-nociceptive treatment, particularly those which inhibit inflammation, given during this period of time (within 4 hours after skin incision) could be considered as preventive treatment targeting the secondary phase of surgical injury. Long-term, painful sequelae following surgical procedures are more common than generally appreciated and even low-level pain can be associated with decreased function. If central sensitisation can be inhibited then there is potential to ameliorate this problem.

Non-opioid analgesics such as NSAIDs and paracetamol (acetaminophen) have proven efficacy both used alone and as a component of a multimodal analgesic regime where they generally reduce opioid consumption by around 30 – 40%. The peripheral and central activity of COX-2 may help to explain the analgesic effects of conventional NSAIDs, which inhibit this isoenzyme, thereby reducing prostaglandin synthesis. However, conventional NSAIDs also inhibit COX-1, the isoenzyme that plays an important role in many homeostatic mechanisms, especially gastrointestinal (GI) mucosal protection and maintenance of normal platelet function and this is the reason for the development of drugs that can preserve COX-1 activity. Since surgical patients are usually fasted, subjected to physiologic stress, and have a potential for bleeding secondary to tissue trauma, the possibility of COX-1 preservation was particularly attractive. This rapidly led to the development and widespread clinical use of coxibs which markedly reduce the risk of upper GI adverse

events and have no effect on bleeding time while still maintaining anti-inflammatory and analgesic efficacy. Despite initial enthusiasm for these drugs, placebo-controlled trials have established that selective inhibitors of COX-2 confer a small but absolute cardiovascular hazard [6]. Recently, the American Heart Association has proposed a ‘stepped-care’ approach to the treatment of patients with concurrent arthritis and heart disease [7]. All NSAIDs inhibit COX-dependent prostaglandin formation but display a wide range of isoform selectivity for COX-2 – with the coxibs at one end of the spectrum and NSAIDs such as naproxen and ibuprofen at the other end. PGI₂ acts as a restraint on endogenous stimuli that promote thrombosis, hypertension, atherogenesis and cardiac damage in vivo [6]. Among these stimuli is the platelet COX-1 product thromboxane (Tx)A₂. However, this is not a simple ‘balance’ but, rather, reflects components of an intricate biological system or network of many mediators. Epidemiological evidence is consistent with the likelihood that diclofenac also confers a cardiovascular risk [6]. An overview of data derived from these trials of chronic administration indicates that myocardial infarction predominates over stroke and that the hazard for myocardial infarction is similar among inhibitors that differ in their degree of selectivity for COX-2 [8]. Mechanistically, this is explicable with respect to the differential impact of these drugs on platelet COX-1-derived TxA₂. Given the nonlinear relationship between inhibition of the capacity of platelets to generate TxA₂ and inhibition of platelet activation in vivo, even drugs such as celecoxib and diclofenac – which inhibit platelet COX-1 to a modest degree (20–30%), transiently during the dosing interval – would be expected to leave platelet function unaffected, as do rofecoxib, valdecoxib and etoricoxib [6].

The likelihood of a cardiovascular hazard is fundamentally related to drug exposure. Concerning short term administration, cardiovascular risk is increased in patients undergoing CABG surgery [9] and they are contraindicated in this group. However, safety concerns identified in studies of CABG surgery appears not to be generalized to the broader surgery patient population [10]. Paracetamol is probably a safer drug but it should be remembered that IG inhibits both COX-1 and COX-2 by 50% [11] and at daily doses >2 g, its GI profile resembles that of tNSAIDs [12].

References:

1. Vane JR. Inhibition of Prostaglandin synthesis as a mechanism of action for aspirin like drugs. *Nature*. 1971; 231:232-5.
2. Hla T, Neilson K. Human cyclooxygenase-2 cDNA. *Proc Nat Acad Sci USA*. 1992; 89: 7384-7388.

3. Koppert W, Wehrfritz A, Korber N, Sittl R, Albrecht S, Schuttler J, Schmelz M. The cyclooxygenase isozyme inhibitors parecoxib and paracetamol reduce central hyperalgesia in humans. *Pain* 2004;108:148-53.
4. Cruickshank AM, Fraser WD, Burns HJ, Van Demme J, Shenkin A. Response of serum interleukin-6 in patient undergoing elective surgery of varying severity. *Clin Sci (Lond)* 1990; 79:161-5.
5. Yokoyama M, Itano Y, Katayama H, Morimatsu H, Takeda Y, Takahashi T, Nagano O, Morita K. The effects of continuous epidural anesthesia and analgesia on stress response and immune function in patients undergoing radical esophagectomy. *Anesth Analg*. 2005; 101: 1521-7.
6. T. Grosser et al., Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities, *J. Clin. Invest.* 2006; 116: 4–15.
7. E.M. Antman et al., Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a science advisory from the American Heart Association, *Circulation* 2007; 115: 1634–1642.
8. P.M. Kearney et al., Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials, *BMJ* 2006; 332: 1302–1308.
9. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoelt A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005; 352:1081-91.
10. Lee Y, Rodriguez C, Dionne RA. The role of COX-2 in acute pain and the use of selective COX-2 inhibitors for acute pain relief. *Curr Pharm Des*. 2005; 11: 1737-55.
11. F. Catella-Lawson et al., Cyclooxygenase inhibitors and the antiplatelet effects of aspirin, *N. Engl. J. Med*. 2001; 345: 1809–1817.
12. L.A. Garcia Rodriguez and S. Hernandez Diaz, Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs, *Epidemiology* 2001; 12: 570–576.

MONITORING OF CARDIO VASCULAR MODIFICATION DURING A TIVA

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Introduction: The TIVA leads to a reversible pharmacological coma where, only using special techniques, (1) the communication between the anesthesiologist and the patient is not possible.

The personal experience, the observation and the interpretation of the clinical signs are many times insufficient to evaluate the impact of the anesthesia on the patient's organism.

The cardio vascular sector is a central element in the maintenance of the vital functions during the anesthesia. For this reason some parameters like the blood arterial pressure (BAP), the heart rate (HR), the quality of the arterial pulsed wave and the capillary filling after the digital decompression, have been and are manual or instrumental methods, to obtain supplementary information on the hemodynamic state of the patient under TIVA.

The evolution of the instrumental technology has introduced in the clinical field, a long series of devices integrating many different technologies. Not all have showed a good degree of performances. But selections the quality of the information obtained, together with an appropriate use and a good interpretation of the data, they allow, in an easy way a diagnosis approach, driven to a therapeutic sequence. The follow up of the cardiovascular parameters evolution can serve to corroborate the good or the wrong therapeutic choice.

The non invasive methods can be simple or sophisticated, with moderate or expensive prices, to be used on a large number of patient or reserved to a selective minority.

However at the moment a minimum equipment is recommended for scientific societies as the American Society of Anesthesiologists (ASA) or the Société Française d'Anesthésie-Réanimation (SFAR), for proceeding with a TIVA and for insuring a correct follow up of the per anesthetic hemodynamic evolution.

These recommendations, without having legal force are considered by the medical experts, acting in legal conflicts, to appreciate the conformity of the equipment.

Respecting the recommendations of the SFAR, an operating room has to have the following elements for a standard hemodynamic monitoring:

ECG monitor, Tensiometer (an automatic one is preferred), pulse Oxymeter and Capnographie.

It is the minimum recommended. However is the information, obtained with the data provided for the cardio vascular standard monitoring, enough to assess the patient hemodynamic status?

Electro cardio scope: With the signals and data derived from this device the HR, the origin of the intra cardiac

electrical stimulation, the rhythm and the stimulus conduction can be detected. That is to say the dependent factors of ionic movement Na^+ and K^+ through the cellular membrane. (Chrono, dromo and batmotropismo).

What for this the informations are interesting?

The Bradycardia, Normocardia or Tachycardia are the three possibilities the HR status. The limits fixed to define each one of these situations are arbitrary and they depend fundamentally on the patient's situation.

For example a HR of 55 b/min., could be tolerated in a patient without heart pathology. However in patients presenting a cardiac "rigidity", the decrease of the frequency could condition a fall of the Cardiac Output (CO) due to the impossibility of increasing the stroke volume (SV).

The tachycardia conditions a decrease of the diastolic period and compromises the lusitropic function. The increase of the myocardial O_2 consumption (MVO₂) and the decreased time for the coronary filling, increase the risk of the per anesthetic myocardial ischemia.

When the intra cardiac electric conduction is modified the synergy of the contraction is modified too with a lost SV, that could be not adapted to the patient's needs.

The pre existent arrhythmias or unchained by the TIVA, drive to hemodynamic modifications that can have important consequences. The lost of the atrial synergy or activity, implies a decrease of until 15% of the diastolic ventricular filling (2). If a bradycardia is presented, the risk of CO decrease to a critical level is a reality.

When a tachycardia accompanies the atrial alteration, a coronary ischemic risk is added, due to the increased MVO₂.

The morphology and the frequency of the ventricle extra systole waves need a particular surveillance. The risk is low when the extra systoles are mono forms and when their frequency is $> 5/min$. The sharp or progressive increase implies the planning of a therapeutic action.

In the case of poly forms extra systoles, a narrow surveillance is needed, since the multiple focuses stimulation, can give place to a re entered phenomenon, developing ventricular rhythms or ventricular fibrillation, when the accompanying conditions are favorable.

In some current monitors it is now day possible, even with a 3 ECG derivations to obtain a continuous monitoring of the ST segment level variations. This one is an interesting information for the precocious detection of per anesthetic myocardial ischemic situation.

Blood Arterial pressure (BAP): The measurement of the arterial pressure has been used from the beginnings of

the specialty to evaluate the patient's heart and vascular reaction during the administration of the anesthesia.

It is a parameter to which all of us are habituated and through it, with a subjective interpretation, we can believe that we are obtaining good information to regulate the conduction of the anesthesia. However it should be remembered that the arterial pressure is the result of an instantaneous inter relationship between the S V and the Vascular Resistances (V R).

Simplifying this concept, when the CO and the BAP are measured, the VR can be calculated.

The consequence of this argument is that the normal or abnormal values of the isolated measure of the BAP, do not inform us if they depend on the balanced, the isolated or simultaneous concordant or divergent modification of the two factors of the BAP generators.

In spite of these critics the measure of the BAP is an important help in the basic monitoring during the general anesthesia.

The BAP non invasives measure methods can be sequential or continuous, manual or instrumental. All they measure an arterial tension that we call pressure for extension, since the measure is obtained thanks to the compression - decompression of the vascular wall.

The simplest manual methods uses a cuff compressive linked to a manometer. Detecting the recovery of the pulse wave, in general on radial artery, during the slow decompression of the pneumatic cuff, the value of the Systolic Arterial Pressure (SAP) is reading on the manometer.

The use of a stethoscope posed on the arterial wall allows the detection of the noises of Korotkoff (4) and therefore an approach to the measure of the SAP but also of the diastolic one (DAP). The differential pressure (Dif AP) can be calculated by a simple subtraction. This parameter, not enough considered during the BAP measurement, gives a lot of informations about patient's cardio vascular status, like it will be seen ahead.

Finally the use of a Pachon's sphygmo manometer, with a Gallabardin's double pneumatic cuff, using the oscillometric principle, allows the manual measurement of the SAP, the DAP, the mean arterial pressure (MAP) and to calculate the Dif AP.

The instrumental methods, can use an ultrasound technique (Arterio Roche MED Cranbury Sounds. NJ. USA), oscillometric one (5) or finger (Finapres Datex - Ohmeda Inc NY USA.) or radial tensiometric one, to measure of the BAP.

All these methods are sequential, except for the finger tensiometric one that offers the possibility of a

continuous acquisition, with the visualization of the arterial pulse curve.

The SAP being the relationship between SV(t). and VR(t), depends from, one side of the ejected SV, which deepens at its own from pre load, contractility and contraction synergy, until that VR is influenced for the elastic characteristics of the arterial tree that can be variably on the time and specifics some vascular sectors.

The DAP implies, during the systolic period, the maximum resistance imposed to the left ventricle to open the aortic valve. However its value corresponds to the effective pressure of the coronary filling which, associated to the coronary flow insures the diastolic myocardial perfusion.

The MAP is the representing pressure value at the interior of the arterial system, in a hemodynamic condition without pulsed flow. The value of MAP implies a static situation that does not guide toward the dynamic variation of the cellular perfusion and overall in some capillary territories (kidney and mesenteric ones for instance) where the circulation is only assured during the systolic pressure pick.

Finally, the Diff AP. offers the possibility to appreciate, in absence of aortic valve pathology, the arterial elastic conditions and subjectively appreciate the SV.

However when the variation of the differential pressure is translated to the morphology of the pulse wave, the analysis of its characteristics reaches all its interest.

Arterial Pressure Pulse Wave:

The systolic and diastolic oscillations of the vascular flow modifying the diameter of the artery walls, generate a pulsed wave that spreads for the whole arterial tree. This wave can be detected manually, given a notion about the HR and cardiac rhythm, as well as of quality of the systolic stroke.

The instrumental visualization of the wave allows to recognize several interesting elements for the cardio vascular monitoring during a general anesthesia.

Represented under the form of a triangular curve, an upward slope, a maximum pick, a descending branch, altered by a dicrotic wave and finally a continuous base line, being prolonged until the next pulsed wave, can be observed.

From the wave morphology it can be suspected an adrenérgica stimulation (rigid upward slope, narrow base, high maximum pick); an increased SV with low VR (wide base, middle high maximum pick); a low SV with low VR (narrow bases with a low maximum pick); or a myocardial failure (narrow base with minimum pick). The variation of the SV, when ventricular arrhythmia or supra ventricular rhythm are presented,

can be verified following up the morphologic changes of the AP wave.

The dicrotic wave, corresponding, to the closing of the valve aortic is observed in the descending slope of the curve. The follow up of its temporal position brings some information concerning the characteristics of the left ventricle systolic expulsion (7). The distance between the beginning of the arterial pulsed wave and the dicrotic one, corresponds to the ventricular ejection time.

On the other hand, if the dicrotic wave is in a lower position, the maximum pick high and the base of the curve wide, it is possible to deduce that the SV is normal or even excessively high, whenever the arterial pressure is normal.

However it is necessary to pay attention to the fact that the time comprised between the dicrotic wave and the beginning of the next arterial pulsed wave corresponds to the diastolic phase and to the coronary filling period. So, if the existing time between the dicrotic wave and the beginning of the new arterial wave is short, coronary perfusion could be impaired over all when a low DAP is observed.

The relationships between the various hemodynamic parameters drive us to the inter dependency cardio vascular parametric notion. The modification of a parameter has to be related with other hemodynamic parameters variations. This fact implicates the correlation of cardio vascular parameters into a hemodynamic profile allowing to detect inter related modification before arrive to a diagnosis and planning a therapeutic action.

The hemodynamic profile: A fairly complete hemodynamic profile needs the integration of data concerning the cardiac output, the pre load, the after load, the myocardial electrical stimulation, the ventricle contractility and the ventricle efficacy. Without forgetting that the aim of the circulation is the correct tissue perfusion, it seems logic to integrate a direct or an indirect information on this fact

A single method is not able, today, to get a complete hemodynamic profile. Even if CO and contractility information can be derived from pulsed arterial wave analysis, or ultrasound method, or bio impedance method, it is necessary to pick up data from satellite devices, completing, in this way, the integration of the hemodynamic profile.

However the appreciations of the pre load, continuous to be a difficult. Even if now days some methods are proposed to be used in the clinical field.

Between them we can cite: The well-known phenomenon of the Delta Up and Delta Down of the arterial pressure wave, under mechanical ventilation (6),

can be used for this end. However its variations could correspond to two different pathological situations. The first one should be a right heart failure. The right ventricle improves some difficulties to fight against increased lung resistances reducing stroke volume during the inspiratory period. The second one detects a hypovolemic syndrome. A test of vascular filling always helps to solve the dilemma. Oscillations are corrected in the event of an altered pre load, persistence in the event of right ventricular failure.

The AP pulsed wave can be obtained by simple methods. A practical one, but the less sensitive, is observation of the signal derived from the pulse oxymeter device. The Finapres system or a similar one, offer the advantage of a continuous BAP measurement. But even a Doppler velocity signal or a compressive arterial wall pulse sensitive device could be employed.

The corrected flow time index (8) seems to take a priority place thanks to its high specific and sensitivity to evaluate pre load status.

Hemodynamic and PetCO₂: When rapid decreases of the CO and/or of the PA are observed, the concomitant modifications of PetCO₂ can be an indicator of an insufficient tissue perfusion and the recovery under a guided therapy, a good index of the effectiveness of the treatment (9-10)

Hemodynamic and Oximetry of Pulse: The variations of the arterial Hb saturation (HbO₂) during the general anesthesia are in the first place linked to the breathing modifications.

In personal observations we have seen that the HbO₂ responded in a delayed way to the hemodynamic variations. An HbO₂ decrease > 10% in relation to the precedent value, determined for a CV modification, is only observed only in serious and dangerous situations.

In summary: The standard hemodynamic monitoring offers multiple possibilities to watch over and to diagnose the per anesthetic modifications.

The data and the signs could be interpreted with the support of solid pathophysiological and clinical notions.

They should always be related to the knowledge appreciation of the patient status for the Anesthesiologist. The patient pathology, the type intervention, to the per operative modification and to the duration of the intervention are all items to be considered to plan not only the anesthesia but even the monitoring system hopping to be used.

The analysis and the interpretation of the modifications of a single parameter are, in general, insufficient. The hemodynamic system is regulated by a series of imbricate and articulate mechanisms.

Systematically we should correct a noxious alteration for a specific patient. However we have to respect, in a certain measure, the modifications well tolerated.

We should treat the patient, not the altered parameter.

A therapeutic action could be established based of the observation of a type of hemodynamic modification.

However the Cardio vascular monitoring is only a guide to the therapeutic election, the dosing and the decision of the use. In any case these facts are always under the Anesthesiologist Medical Doctor responsibility.

Bibliography:

- 1) Muchada R, Lucchesi G. Endarterectomía carotídea bajo Remifentanilo. Rev.Esp. Anesthesiol. Reanim. 2001;48:508-512.
- 2) Pagel PS, Khel F, Gare M et al. Fonction mécanique de l'oreillette gauche Cah. Anesthesiol 2004 ;52 :101-112.
- 3) Kaplan J A, King S B. The precordial electrocardiograph lead (V5) in patients who have coronary artery disease. Anesthesiology 1976;45: 570-574.
- 4) Kirkendall W M, Burton A C et al. Recommendation for human blood pressure determination by sphygmomanometers . Circulation 1967; 85:980-996.
- 5) Francousal M, Himmich H et al. Evaluation d'une méthode oscillométrique de mesure automatique de la pression artérielle. Agressologie 1980 ;21 :157-161.
- 6) Marx G, Cope T, Mc Crossann L et al. Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. Eur.J Anaesthesiol. 2004;93:782-788.
- 7) Allaria B, Dei Poli M, Brunetti B et al. New concepts in low invasive intraoperative cardiovascular monitoring. Acta Anaesthesiol. Scandinavica 1989: S91, 33,A19.
- 8) Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 1997, 315:909-912.
- 9) Tournadre J P, Moulaire V, Barreiro G, Muchada R et al. Simultaneous monitoring of non invasive hemodynamic profile and capnography for tissue perfusion evaluation. J. Anaesth. 1994;8:400-405.
- 10) Tonnessen T I. Biological basis for pCO₂ as a detector of ischemia. Acta Scand. Anaesthesiol. 1997;41:659-669.
- 11) Brunel D, Muchada R. Evaluation de la perfusion tissulaire par la surveillance simultanée

du débit aortique et de la capnographie. Press. Med.1991;34 :1665-1666.

STARCH VERSUS GELATINS

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During (hypovolemic-related) low output the organism tries to compensate perfusion deficits by redistribution of flow to vital organs resulting in an underperfusion of splanchnic bed, kidney, muscles, and skin. Volume therapy is aimed to restore abnormal tissue perfusion and oxygenation. However, this process may result in additional problems defined as re-perfusion injury. Release of several inflammatory mediators including oxygen radicals is involved in damaging endothelial membrane integrity. There is increasing evidence that the choice of the ideal plasma substitute for treating hypovolemia goes beyond the simple haemodynamic effect. Perioperative fluid optimization represents an approach to limit the incidence and severity of systemic inflammation and organ dysfunction following major surgery. In contrast to HES, there are only sporadic reports exploring the effects of gelatins on inflammation and endothelial injury. The current tendency is to infuse colloid solutions rather than large amounts of crystalloids. HES possesses several advantages in this patients and has become a widespread volume replacement strategy.

TIVA – TCI TECHNIQUES, THE CURRENT SITUATION IN CHILE

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The first documented report with TIVA-TCI was from a patient done in March 12th, 1998 in Santiago's Clinica Alemana, a complex private hospital. The first ten Diprifusors® had arrived that week and by the next morning, TIVA started at the biggest academic hospital in the country, the University of Chile Clinical Hospital.

Since then, the practice of intravenous anesthesia has grown exponentially.

Aprox. 60000 TIVA procedures are administered each year representing 12% of all general anesthetics. More than 130000 mg of remifentanil are consumed each year, representing almost 25% of all procedures under general anesthesia. Several meetings and refreshing courses have been dictated, in the capital city and abroad. More than 1150 anesthesiologists have received training in TIVA.

There are 30 national publications regarding TIVA in peer-reviewed and non peer – reviewed journals, together with abstract presentations in international meetings. 2 books in Spanish have been published specifically about TIVA, with more than 13500 units sold within South America.

There is a TIVA software developed completely by national experts, the ANESTFUSOR® that is currently in phase III experiment.

The use of this more sophisticated and more expensive anesthetic technique is widely spread in this developing country. Almost every anaesthesiologist in has received specific training about it, half of them has participated in workshops. Almost 50% of the received one of the 2 TIVA books available. There are TIVA pumps in 30% of every OR in the country. In some private hospitals TIVA is 80% of all general anesthesia procedures.

TIME TO PEAK EFFECT

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With a pharmacokinetic model the time course of the plasma concentration can be described and predicted based on a given drug input. These parameters can be used in Target controlled infusion (TCI) systems for controlling the infusion rate. For several reasons the first commercially available TCI system was designed to control the plasma concentration - that is, the target was the plasma concentration.

In clinical practice the anesthesiologist attempts to reach the drug effect as fast as possible not only during induction but also during the course of an anesthetic if more drug effect is required. It is common sense that the drug has to move to an effect site before it can exert its intrinsic effect. It is also obvious that there is some time delay between the time course of the plasma concentration and the time course of some (hypothetical) concentration at this effect site. Based on this observation in data of the muscle relaxant Pancuronium, in 1978 Hull et. al.¹ introduced the idea of a biophase compartment. With this additional compartment they attempted to account for this observed time lag between the time course of plasma concentration and the effect. Because this compartment was treated as a „true“ compartment the parameters of the pharmacokinetic description had to be recalculated. Contemporarily Sheiner et.al.² also used an effect compartment for modeling the effect of d-tubocurarine.

With their concept only one additional parameter (ke_0) was used for describing the time course of the effect site concentration. Therefore with 7 parameters, the time

course of the effect site concentration can be described for a drug with 3 compartment pharmacokinetic characteristic. This model for the effect site is also called the link model because it links the time course of the plasma concentration with the model for the concentration effect relationship.

It is desirable to extend the TCI technology from control of plasma concentration to control of effect site concentration. Therefore, if for such a system a well-established pharmacokinetic model is available, it is tempting to combine this model with a good link model (ke_0 value). Unfortunately, if this link model is derived from another study, the ke_0 is only valid for the pharmacokinetic parameters derived in the same study. Since the ke_0 value eventually is only one of the seven parameters of the overall description of the effect site concentration its applicability is limited to be used together with the other 6 pharmacokinetic parameters. Therefore, using a ke_0 value from one study together with pharmacokinetic parameters from another study is unreasonable as e.g. exchanging Cl_2 of one parameter set with the one from another experiment.

Time to peak effect site concentration is a unique descriptor of the onset of drug effect.³ The goal of targeting the effect site concentration is to reach the effect as fast possible with no overshoot. This goal is achieved if the TCI system reaches the predicted target concentration at the time of peak effect. Therefore, for combining the pharmacokinetic parameters with pharmacodynamic data of another study, the time to peak effect has to match. It would be only by chance that the combination of the pharmacokinetic parameters with the ke_0 of another study will provide with an appropriate time to peak effect site concentration. If one trusts the pharmacodynamic data of a study (that is the t_{peak}) and wants to combine this information with well-tested pharmacokinetic parameters, a ke_0 value can be estimated for this purpose.

For estimating the ke_0 value in combined pharmacokinetic-pharmacodynamic a so-called loop-collapsing method can be used. The study most often involves a constant infusion of brief duration until the maximal effect is achieved. The hysteresis between the time course of the measured plasma concentration and the effect is subject to this “collapsing” procedure. Based on the complete model for the effect site concentration, with simulation the time of peak effect site concentration after a bolus dose can be calculated. Experimentally the time to peak effect site concentration can be measured only if a sub maximal bolus dose is given. This measured time on the other hand can then be used to estimate the corresponding ke_0 value based on the pharmacokinetic description. Struys et. al.⁴ used in a study with propofol the measured time of peak effect from the study of Schnider et. al.⁵ and combined it with

the parameter of Marsh et. al.⁶ for targeting the effect site concentration successfully.

Time to peak effect (site) concentration is a unique descriptor of the onset of drug effect. Since ke_0 values cannot be combined with the pharmacokinetic parameters of other studies, with t_{peak} it is possible to calculate an appropriate link model for any pharmacokinetic model. If a full PKPD model from a single study is not available, a combined model for the effect site can be used alternatively for TCI systems.

References:

1. Hull CJ, Van Beem HB, McLeod K, Sibbald A, Watson MJ: A pharmacodynamic model for pancuronium. *Br.J.Anaesth.* 1978; 50: 1113-1123.
2. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin.Pharmacol.Ther.* 1979; 25: 358-371.
3. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; 99: 324-33.
4. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment versus two methods for effect compartment--controlled target-controlled infusion for propofol. *Anesthesiology* 2000; 92: 399-406.
5. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90: 1502-16.
6. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. *Br.J.Anaesth.* 1991; 67: 41-48.

IS THERE LIFE BEYOND KE_0 ?

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In practice (intravenous) anaesthesia seems deceptively simple: based on a trained dosage scheme the anaesthesiologist gives a certain amount of drug and, while observing the effect, after a while he decides if this dose was right, too much or too little and whether or not he should adjust the pre-planned dosing scheme with which anaesthesia was started.

This is a kind of closed loop process where the effect is the output variable (what ever that may be) but with two input variables: the dose and the time to wait before the effect is judged. The appropriate dose and the range in which to expect the right dose can be trained, time as variable however is a much more complicated matter.

Quite often in clinical practice it is not the dose that was wrong but the time to wait for the (side) effects. For example: apnoea on the ward after loading with morphine or methadone in the recovery¹ or too early stimulation with the laryngoscope leading to increase drug administration and delayed side effects or the opposite: a patient starting breathing again after a flush of remifentanyl in the recovery room even before artificial ventilation has commenced.

Having knowledge about the delay between a dose, either bolus or infusion, and the time to expect the effect is maybe as important as having knowledge about the appropriate quantity of the dose.

With the coming of Target Controlled Infusion a more rational approach of anaesthetic drug dosing became possible as opposite to the intuitive manual dosing techniques. The anesthesiologist can set a blood target and at the same time is informed on the drug concentration in the theoretical effect compartment. Anaesthesia does not take place in the blood but somewhere at the effect site. Changes in the blood concentrations will be followed by a change of concentration at the effect site but with a delay that is typical for the drug.

This technique can even be taken a step further: instead of taking the theoretical blood concentration as a target the desired concentration at the theoretical effect site can be the aim of control in a TCI system.

In all the aforementioned cases the delay between change in blood concentration and change in effect is extremely important. In compartmental modeling the delay is specified by a timeconstant: $ke_0(\text{min}^{-1})$. With this ke_0 the time delay of drug transport between the central compartment and a theoretical effect compartment is described. The theoretical effect compartment has an infinitely small volume so that it does not take part in the pharmacokinetic equations in terms of the mass balance of drug moving in and out of the compartments. The drug concentration in the effect compartment can be related to the effect, time independently, using a model appropriate for the drug response: for example: a linear, Emax or Sigmoid Emax model.

As the concentration in the effect compartment cannot be measured directly, the ke_0 has to be determined indirectly. In many of the following methods a pharmacokinetic model is used to fit or predict the related blood concentrations. If this is the case than the

resulting ke_0 becomes part of the pharmacokinetic model.

There have been several methods developed to estimate the ke_0 :

1. Hysteresis

This technique requires continuous measurement of drug effect for example with derivative of the EEG like the Bispectral Index (BIS), Auditory Evoked potential (AEP), Median frequency, Cerebral state index(CSI), entropy, spectral edge, Canonical univariate parameter(CUP). A continuous infusion is delivered until the maximum effect is obtained in all study subjects. Then the infusion is stopped. The blood concentration plotted against the effect, shows a typical hysteresis curve. The concentration in the effect compartment is calculated in such a way that the hysteresis disappears. There is no information required on the nature of the effect, the maximum or minimum effect or the steepness of the response. If no assumptions are made on the pharmacokinetic model that underlies the blood concentration then this is called the nonparametric approach. Ke_0 derived this way can be used by different pharmacokinetic models. It then depends on the ability of the pharmacokinetic model to predict the changing blood concentration accurately whether this connection between nonparametric ke_0 and pk model produces sensible results.

It is also possible to fit a pharmacokinetic model to the measured blood concentrations of the individual or the research group. This is the individual or group parametric approach. Blood sampling should be appropriate for building such a model, which is not always the case (see 14 in table).

Lastly a known pharmacokinetic model can be selected to produce the blood concentration as a result of the drug dosing the actual measured concentrations are neglected. In this situation some errors of the pharmacokinetic model are more or less corrected by the ke_0 .

2. Time to peak effect

Not so long ago another approach has been proposed to calculate the ke_0 . Again a continuous measurement of drug effect is required. A bolus dose is given that produces sub-maximum effect. Then the time is measured at which the effect peaks(TPE). From this time the ke_0 can be derived⁴. Usually the derived ke_0 is a parametrically scaled parameter or in other words a pharmacokinetic model is used for which the ke_0 then forms the Pk/Pd link parameter. As the TPE is in theory a model and dose independent observation it could be simply used to estimate the ke_0 in different Pk/Pd models.

Published ke_0 values however show that this technique is less straight forward than it seems on first glance.

3. The pharmacodynamic response model

Most commonly anaesthetic drug effect is best described by a sigmoid E_{max} model. If it is possible to parameterize such a model then this can be used to estimate the ke_0 value. A continuous measurement of effect again is required. The complexity and number of estimated parameters require careful study design with often multiple changes in the dose to quantify the parameters. The advantage of the technique is that the parameters estimates may include coefficients of variation so that accurateness of the model can be assessed. Furthermore it allows to study the parameters in the context of special application: for example Target Controlled Infusion.

4. Dose modulation

It is obvious that with different speeds of input the effect site concentration will reach a certain concentration at different time points. Assuming that the ke_0 is constant and not rate dependent then this time difference can be used to calculate the ke_0 . Advantage is that clinical discrete endpoints like loss of consciousness or loss of eye lid reflex can be used and no surrogate continuous measurement is required. Speed of drug input can be modulated by infusion rate or by using different drug dilutions. Even more advanced techniques are possible whereby the calculated concentration in the blood or at the effect site is ramped up with different angles using computer controlled infusion techniques. If different rates cannot be repeated in the same subject then this technique only allows estimating the population ke_0 .

Studying PK/PD of anaesthetic drugs is a very complex matter. Usually one can find only a few publications that describe the complete Pk/Pd including ke_0 of an anaesthetic drug. The exception is Propofol. Different formulations, new drug development, inconsistencies between research results and clinical observations have initiated many studies on the Pk/Pd of propofol. If only the studies that describe or verify the ke_0 are taken into account then over the last decade more than fifteen studies can be found that in one way or the other studied and tried to quantify the ke_0 of propofol. From a clinical point of view it is quite disappointing that the ke_0 's reported in these studies are not very consistent(table). The used methodology seems to have a major influence on the value but also the used surrogate effect measurement (table,13), drug formulation (table,14) and maybe even rate of administration (table,17) or time course of administration.

On top of this 'inter-study' variability there is, maybe not surprisingly, also a large 'intra-study' variability.

Very few studies are available that compare the calculated concentration in the theoretical effect compartment with a clinical effect^{2 3}. And although we have commercially systems available that allow the

anesthetist to control the effect compartment there are even less studies that evaluate the usefulness or possible pitfalls of these systems.

Possibly a few patterns can be recognized in the diversity of study results although this statement has to be made with caution.

1. Löttsch, Rafael Dudziak, Rainer Freynhagen Jürgen Marschne, Gerd Geisslinger. Fatal Respiratory Depression after Multiple Intravenous Morphine Injections. Clin Pharmacokinet 2006; 45 (11): 1051-1060

2. Sutcliffe N, Hay A, Jack E, McCormick M, Litchfield K, Engbers F, Schraag S Relationship of predicted propofol effect-site concentrations with EEG based markers of anaesthetic depth: Relevance of model selection. Anaesthesia: in publication

3. S.E. Milne1, A. Troy, M.G. Irwin and G.N.C. Kenny, Relationship between bispectral index, auditory evoked potential index and effect-site EC50 for propofol at two clinical end-points. British Journal of Anaesthesia 90 (2): 127±31 (2003)

4. Minto CF, Schnider TW, Gregg KM et al. (2003) Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. Anesthesiology 99:324–333

and intravenous infusions, Schnider et al. found that the rate of equilibration was rapid, with a half-time of equilibration, $t_{1/2 ke0}$, of 1.5 min, and a peak effect, t_{peak} , of 1.7 min³. Schnider's finding of rapid equilibration was subsequently validated by Struys et al⁴. However, using continuous infusions of propofol, Doufas et al found a much slower rate of plasma-effect site equilibration, with a $t_{1/2 ke0}$ of 4.1 min, and a t_{peak} of 2.7 min. They also found that infusion rate had no influence on ke_0 .⁵ The maximum propofol infusion rate in the study of Doufas et al was 60 mg / min, far lower than the maximum rate of approximately 500 mg/min required for Schnider and colleagues to give a 2.5 mg bolus over 20 seconds. Doufas et al proposed that there could be a fundamental difference in plasma-effect site equilibration depending on whether propofol was given as a bolus or continuous infusion.⁵ In this lecture, we will show if and how the rate of propofol administration influences the pharmacokinetics and dynamics of propofol. If so, this must be considered when designing drug infusions, and is particularly relevant for target controlled infusion systems.

1. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther 1979; 25: 358-71

2. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the Time of Maximum Effect Site Concentration to Combine Pharmacokinetics and Pharmacodynamics. Anesthesiology 2003; 99: 324-333

3. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502-16

4. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment versus two methods for effect compartment--controlled target-controlled infusion for propofol. Anesthesiology 2000; 92: 399-406

5. Doufas AG, Bakhshandeh M, Bjorksten AR, Shafer SL, Sessler DI: Induction speed is not a determinant of propofol pharmacodynamics. Anesthesiology 2004; 101: 1112-21

	Ke0	T1/2ke0	TPE	Publication	Connected Pk model	Population	Methodology	Measurement
1	0.2	3.47		Billard, Clin Pharmacol Ther 1997; 61:45-58	7		Hysteresis	Bis
2a	0.267	2.6	3.87	Abstract world congress Australia 1996	Marsh/Implemented in TCI systems	22 male patients		AER
2b	0.16	4.3		White et al; Br J Anaesth 1999;82:333-9				
2c	0.17	4.07						
2d	0.24	2.8						
3	0.8	0.866	2.07	Lim; Br J Anaesth 91 (5): 730-2 (2003)	Marsh	3*75 patients	Combination of bolus and infusions	Assumed equal Cp50 LOC
4	0.57	1.22	2.53	Lim; J Anesth (2006) 20:153-155	Marsh	2*18 patients	2 targets in TCI	Assumed equal Cp50 LOC
5	0.63	1.1	1.88	Wakeling, Anesthesiology; 98(1):92-97	Study model	20 patients	Keo estimated and verified comparing Effect TCI and TCI	Assumed equal LOC
6	0.12	5.7	3.7	Jensen Anaesthetist 2006;55:633-642	Study model individual parametric	10 male patients	Sigmoid Emax model fitted to ramp-up and clamped effect	Median frequency EEG
7	0.21	3.3	3.6	Fechner Anesthesiology 2004; 101:626-639	Study model individual parametric	9 male volunteers	Sigmoid Emax model fitted to ramp-up and clamped effect	Median frequency EEG/BIS
8	1.32	0.57	1.6	Struys; Anesthesiology 2000;92:399-406	Marsh	40 patient	Effect site control with keo based on Time to Peak effect of 1.6 min	Bis
9	0.456	1.52	1.7	Schnider; Anesthesiology 1999;90(6):1502-16	Schnider Implemented in TCI systems	24 volunteers	Time to peak effect (TPE)	cononical univariate parameter (CUP)

THE INFLUENCE OF INFUSION RATES ON THE PK/PD OF PROPOFOL

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Propofol transfer between the plasma and effect-site can be modelled as a first-order process characterized by ke_0 1,2. The standard model of ke_0 assumes that the rate of equilibration between the plasma and the site of drug effect is independent of the rate of drug administration. However, there are conflicting data on the rate of equilibration between the plasma and the site of propofol drug effect. In a study involving both bolus injections

NEUROMUSCULAR REVERSAL

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Neuromuscular blocking drugs (NMBDs) introduced in clinical anesthesia in 1942, are used to facilitate endotracheal intubation and provide skeletal muscle relaxation during surgery. In the last two decades we have witnessed the introduction of a number of new nondepolarizing NMBDs into clinical practice such as vecuronium, rocuronium and cisatracurium. These modern intermediate-acting agents have important clinical advantage if compared to the older long-acting drugs such as d-tubocurarine and pancuronium.

Despite apparently adequate clinical reversal with acetylcholinesterase inhibitors (neostigmine, edrofonium) the frequency of residual block, defined as a train-of-four (TOF) ratio < 0.7 , was also noted after the use of the intermediate-acting NMBDs.

It is clear that no substantial progress has been made in the field of neuromuscular reversal. Up to now, neostigmine is still the most common drug used despite the well known unwanted effects of cholinesterase inhibitors.

Because of their site of action, administration of anticholinesterases can result in cardiovascular (heart rate and blood pressure changes, dysrhythmia), gastrointestinal tract (increased motility and secretion of gastric fluid and acid), increased risk of emesis and respiratory (bronchoconstriction) effects, arising from non-specific activation of nicotinic and muscarinic synapses. Muscarinic antagonists (atropine or glycopyrrolate) are used for prevention of muscarinic side-effects of the anticholinesterase drugs but are also associated with side effects relating to their function.

Omitting antagonism, however, introduces a non-negligent risk of residual paralysis, even with short-acting NMBDs.

Neostigmine, like other anticholinesterases, can not reverse a profound nondepolarizing blockade and has a ceiling effect, so reversal of NMBD is usually done by waiting until recovery of twitch height to 10-25% in order to avoid an inadequate recovery of neuromuscular function. This is the reason why succinylcholine is still used in current anesthetic practice, especially for rapid sequence induction and short surgical procedures.

Few experimental studies have been made to investigate the nonclassic reversal drugs. In this regard, suramin, a P2-purinoceptor antagonist, can reverse NMBDs but some deleterious side effects were found during the clinical use. Other two drugs were explored: the first one was the purified human plasma cholinesterase used to antagonize mivacurium-induced neuromuscular blockade and the second one was cysteine that has been shown to reverse the neuromuscular blocking effects of gentacurium.

An ideal reversal drug should facilitate rapid and complete reversal at any level of neuromuscular blockade without muscarinic effects and an improved side-effect profile.

Recent reports have described the use of cyclodextrins to reverse rocuronium-induced neuromuscular block with the new pharmacological concept of inactivation through complex formation.

Sugammadex, a modified γ - cyclodextrin was recently selected for clinical development and was found to be effective and well tolerated in healthy volunteers. This molecule is not a real reversal drug, but rather a selective relaxant binding agent that was engineered to bind rocuronium bromide forming a tight complex with the hydrophobic steroid skeleton of rocuronium in a 1:1 ratio. The advantage of using cyclodextrins as NMBD reversal agents is that they are generally water soluble, have no endogenous targets, and are therefore unlikely to cause major side effects.

Sugammadex has the ability to terminate the action of NMBDs quickly and at any level of block and this should make surgical care much easier and safer.

Will sugammadex replace the currently used combinations of anticholinesterases and muscarinic blocking drugs? It will probably depend on pharmacoeconomic considerations as well as on comparative effects of these reversal drugs at less profound levels of residual neuromuscular blockade.

RESIDUAL PARALYSIS: EPIDEMIOLOGY, CONSEQUENCES, TREATMENT

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Post-Operative Residual Curarization (PORC) is the tracheal extubation in the presence of residual paresis and can contribute to post-operative complications including respiratory events. A review on PORC (1) listed several studies reporting an incidence of residual paresis between 20 and 50%. Some epidemiological studies have identified inadequate reversal as an important cause of post-anesthetic mortality (2). It has been demonstrated that the incidence of post-operative respiratory complications was significantly higher in patients who had residual paresis in Recovery Room (3). It has also been hypothesized that the clinical duration of neuromuscular blocking drugs could be associated with incidence of PORC: in a study (4) it was shown that incidence with pancuronium, atracurium and vecuronium was, respectively, of 41 - 9 - 11% in patients who had adequate spontaneous respiration after

reversal of neuromuscular blockade. Thus, the choice of relaxant might be important and the presence of adequate spontaneous respiration does not guarantee the complete reversal of neuromuscular block, especially of the smaller muscles such as the extraocular muscles, the adductor pollicis, and the muscles of the larynx and pharynx responsible for airway protection and swallowing. The diaphragm recovers from the effects of non-depolarizing muscle blockade more rapidly than the small muscles of the larynx, the pharynx and the adductor pollicis. Reduced cardiopulmonary reserve and effects of narcotics, sedatives and other anesthetic drugs can potentiate the morbidity and mortality of PORC.

For many years a train-of-four ratio (TOFR) of 0,7, measured at the thumb, was considered an adequate recovery; recent study have documented that this TOFR does not guarantee sufficient recovery and normal muscle vital function, including normal pharyngeal function, request TOFR at the thumb > 0,9 (5).

How then we can evitate the PORC? First long-acting neuromuscular blocking agent should not be used, but prefer the intermediate-acting or short-acting by boluses or both in continuous infusion under monitoring of the depth of neuromuscular block and with a muscular block of 90-92%. Second, the reversal should not be employed before two responses to TOF stimulation are present. Third, administer the right dose of neostigmine (about 0,05 mg/kg) and wait for the time to peak effect (5-8 min). Fourth, avoid body hypothermia that slows down the elimination of neuromuscular blocking drugs.

A new drug, Org 25969 o Sugammadex, a γ -cyclodextrine, englobe the molecules of rocuronium inactivating them and producing a rapid, complete and lasting reversal of muscular block by rocuronium.

In conclusion, the PORC is an important problem in the post-operative period and the monitoring of neuromuscular transmission and the use of intermediate- o short- acting neuromuscular blocking drugs lowers incidence of PORC but not eliminate it. Thus, all patients who received neuromuscular blocking drugs should be closely monitored for several minutes (20-30) in the recovery room, where any episode of airway obstruction o ventilatory inadequacy can be rapidly and effectively treated.

Bibliography:

- 1) Bevan, DR; Donati, F; Kopman, AF. Residual neuromuscular blockade. *Anesthesiology* 1992; 77: 785-805.
- 2) Cooper, A. L., Leigh, J. M., Tring, I. C. Admissions to the Intensive Care Unit After Complications of Anaesthetic Techniques Over 10 Years. 1. The First 5 Years. *Anaesthesia* 1989; 44 : 953-8.

- 3) Berg, H., Roed, J., Viby-Mogensen, J., et al. Residual Neuromuscular Block Is a Risk Factor for Postoperative Pulmonary Complications. A Prospective, Randomised, and Blinded Study of Postoperative Pulmonary Complications After Atracurium, Vecuronium and Pancuronium. *Acta Anaesthesiol Scand.* 1997; 41: 1095-1103.

- 4) S. Ghosh-Karmarkar, J.V. Divatia, A.P. Kulkarni, V.P. Patil, P. Mehta. Residual Neuromuscular Blockade in the Recovery Room : Does the Choice of the Muscle Relaxant Matter? *J Anaesth Clin Pharmacol* 2006; 22: 29-34.

- 5) Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology* 1997; 86: 765-71.

PHARMACOLOGY AND CLINICAL USE OF CYCLODEXTRINS

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Cyclodextrins comprise a family of cyclic oligosaccharides. They were initially obtained as degradation products of naturally occurring starch in the nineteenth century. Several members of this family are used in industrial and pharmaceutical applications because they can form water soluble complexes with insoluble chemical entities. The common cyclodextrins contain 6, 7 or 8 glucose units, and are designated as α , β and γ respectively. Their molecular weights are 973, 1135 and 1297 respectively. Their three-dimensional structures resemble a hollow or a doughnut 1. They have been already used in anaesthesia to formulate different agents used in anaesthesia including propofol, etomidate, bupivacaine, sufentanil or intranasal midazolam. α , β and γ cyclodextrins have been tested in vitro to reverse rocuronium-induced neuromuscular block in isolated mouse hemi diaphragm 2. Their potency is well correlated with the cavity size. Only γ cyclodextrins have a cavity large enough to reverse rocuronium NMB. The cavity size must have a diameter of 7.5 – 8.3 Å 3. Cyclodextrins have a lipophilic centre but a hydrophilic outer core. Several modified γ cyclodextrins were tested with rocuronium. The addition of eight side chains has led to an extension of the cavity and a better link with the four hydrophobic steroidal rings of rocuronium to form an inclusion complex. Sugammadex is a γ cyclodextrin specifically designed to encapsulate rocuronium. Addition of negatively charged carboxyl groups at the end of the 8 side chains enhance electrostatic binding with the positively charged

quaternary nitrogen of rocuronium. These groups are very important to maintain the high water solubility of the resulting host molecule; Interactions, due to van der Waal's forces, hydrophobic and electrostatic mechanisms produce a tight and long-lasting complex between one molecule of sugammadex and one molecule of rocuronium. The association constant of sugammadex to rocuronium as tested by isothermal titration calorimetry is very high, about (10^7 M⁻¹), whereas the dissociation rate is very low 3,1.

When sugammadex is introduced in blood, the free molecules of rocuronium in plasma which are in equilibrium with the tissues are almost immediately captured by the sugammadex molecules and the plasma free rocuronium concentration decreases very rapidly. This creates a gradient of rocuronium between tissue and plasma, with rocuronium molecules moving out of the tissue and into plasma where they are encapsulated by free sugammadex molecules. The diffusion of sugammadex onto the tissues and formation of complexes at the neuromuscular junction remains discussed. Following administration of sugammadex, the concentration of free rocuronium decreases rapidly in the plasma but the total rocuronium plasma concentration (free and bound to sugammadex) increase rapidly 4. Then, the complex will be rapidly filtered by the glomerulus and eliminated through the kidney. In summary, sugammadex is not an antagonist of NMBA as neostigmine or edrophonium which act on acetylcholinesterase. Sugammadex has no direct effect on cholinergic transmission. It is considered as a selective relaxant binding drug (SRBA). Sugammadex does not exhibit intrinsic biological activity.

Sugammadex has been tested in several animal models including guinea pigs, cats and monkeys to investigate its properties for the reversal of non depolarizing muscle relaxant- induced block. Sugammadex selectively reverses steroidal NMBA, particularly rocuronium but also vecuronium and pancuronium. Its selectivity for steroidal NMBA over atracurium or succinylcholine is due to the size of its inner cavity and its structural complementarity with the right hydrophobic steroidal skeleton. It does not have any affinity for more than 40 drugs that may be used during anaesthesia (hypnotics, analgesics, antibiotics, cardiovascular drugs). Affinity for cortisone, hydrocortisone, aldosterone has been extensively studied because sugammadex binds strongly to steroidal NMBA, affinity is 120 fold less than for rocuronium. Affinity for atropine, verapamil, ketamine is 400 to 700 fold lower than for rocuronium. Among many molecules studied, toremifene and flucloxacillin are the only molecules known to displace rocuronium or vecuronium. In monkeys, sugammadex has a very rapid onset of action. It produces 90% reversal from rocuronium-induced neuromuscular block in less than 3 minutes. The recovery time to a 0.9 TOF ratio after

spontaneous recovery was 14.4 min and was reduced significantly to 1.9 min with 1.0 mg/kg sugammadex 5. Reversal of atracurium induced NMB was not effective. In another study reversal of profound rocuronium-induced neuromuscular block, spontaneous recovery time to a 0.9 TOF ratio took 28 min. It was reduced to 8 min after 2.5 mg/kg sugammadex. No signs of residual blockade or recurarisation were observed 6.

In volunteers, administration of 8 mg/kg sugammadex 3 min after 0.6 mg/kg rocuronium resulted in the recovery of a 0.9 TOF ratio within 2 min 7. A phase II study, in adult patients, has shown that sugammadex, administered at reappearance of T2 of the TOF reversed 0.6 mg/kg rocuronium-induced neuromuscular block in a dose-dependant manner. At doses of sugammadex at or above 2.0 mg/kg recovery occurred within 3 min without any sign of recurarisation. Sugammadex increased the proportion of the rocuronium doses excreted unchanged in the urine from 19% to approximately 50% 8. Moreover, 2 – 4 mg/kg sugammadex when given at reappearance of T2 in prolonged rocuronium-induced block (> 2 h) effectively reversed rocuronium. Increasing sugammadex from 0.5 to 4 mg/kg shortened the time needed to attain a 0.9 TOF ratio from 6.8 to 1.4 min 9. Profound neuromuscular block (Post-tetanic count: 1 or 2) can be rapidly and safely reversed with sugammadex in humans. With 4 or 8 mg/kg, a 0.9 TOF ratio could be obtained in 3.3 min (range 2.2 – 4.7 min) and 1.5min (1.0 – 2.1 min) respectively 10. Although sugammadex was developed to antagonise rocuronium-induced block; it is also effective in reversing 0.1 mg/kg vecuronium-induced block. When given at reappearance of T2, recovery of a 0.9 TOF ratio was obtained in 2.3 min and 1.5 min following 2.0 and 4.0 mg/kg respectively 11

Up to now, approximately 1500 patients have received sugammadex. Most of the related side effects are unspecific including hypotension, movement coughing, dry mouth or nausea. Prolongation of the corrected QT interval have been described but with the same rate than in the placebo group. This can be observed with several anaesthetic agents; therefore its signification is questionable.

Sugammadex is a very exciting drug because it can reverse easily and rapidly any level of rocuronium-induced neuromuscular block when given at the appropriate dose. The use of sugammadex could make anaesthesia much easier and safer. It would become possible to reverse the block exactly when needed. No residual paralysis should be observed in the recovery room. The recommended dose in adults should be 2 mg/kg when given at T2 and 4 mg/kg in deep block when there are only few responses at the PTC. Although yet under investigation high doses (16 mg/kg) given 3 min after rocuronium could reverse rapidly its effects.

As pointed by Jennifer Hunter/ Its variability of effects still need to be ascertained in large number of patients, however, and we await the almost inevitable side effects: no perfect drug exists. Nevertheless, we are on the threshold of another exciting development in neuromuscular pharmacology 12.

Reference:

1. Naguib M: Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesthesia Analgesia* 2007; 104: 575-81
2. Zhang MQ: Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? *Drugs Future* 2003; 347-54
3. Bom A, Bradley M, Cameron K, Clark JK, Van Egmond J, Feilden H, MacLean EJ, Muir AW, Palin R, Rees DC, Zhang MQ: A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew.Chem.Int.Ed Engl.* 2002; 41: 266-70
4. Epemolu O, Bom A, Hope F, Mason R: Reversal of neuromuscular blockade and simultaneous increase in plasma rocuronium concentration after the intravenous infusion of the novel reversal agent Org 25969. *Anesthesiology.* 2003; 99: 632-7
5. de Boer HD, Van Egmond J, van de PF, Bom A, Booij LH: Sugammadex, a new reversal agent for neuromuscular block induced by rocuronium in the anaesthetized Rhesus monkey. *British Journal of Anaesthesia* 2006; 96: 473-9
6. de Boer HD, Van Egmond J, van de PF, Bom A, Booij LH: Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. *Anesthesiology.* 2006; 104: 718-23
7. Gijsenbergh F, Ramael S, Houwing N, van Iersel T: First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology.* 2005; 103: 695-703
8. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, Viby-Mogensen J: Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. *Anesthesiology.* 2006; 104: 667-74
9. Shields M, Giovannelli M, Mirakhor RK, Moppett I, Adams J, Hermens Y: Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. *British Journal of Anaesthesia* 2006; 96: 36-43
10. Groudine SB, Soto R, Lien C, Drover D, Roberts K: A randomized, dose-finding, phase II study of the selective relaxant binding drug, Sugammadex, capable

of safely reversing profound rocuronium-induced neuromuscular block. *Anesthesia Analgesia* 2007; 104: 555-62

11. Suy K, Morias K, Cammu G, Hans P, van Duijnhoven WG, Heeringa M, Demeyer I: Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology.* 2007; 106: 283-8

12. Hunter JM, Flockton EA: The doughnut and the hole: a new pharmacological concept for anaesthetists. *British Journal of Anaesthesia* 2006; 97: 123-6

NEW DEVICES IN TIVA-TCI: THE POINT OF VIEW OF THE FDA

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Total intra-venous anesthesia (TIVA) uses target controlled infusions (TCI) pumps. A recent development in this area is the closed-loop control of TIVA. The kind of "feed-back" information that is necessary to effectively control a closed-loop TIVA system is currently an open question. For regulatory purposes, the US considers the TCIs used in close-loop controlled TIVA, medical devices. Those devices are regulated by the Center for Devices and Radiological Health (CDRH) at the US Food and Drug Administration (US FDA). Dr. Schultz will present US FDA's approach to regulating medical devices and discuss similarities and differences from the EU. He will address current views on total intravenous anesthesia (TIVA), including closed-loop control of TIVA.

WHY TCI IS NOT AVAILABLE IN THE USA AND THE REGULATORY PATH FORWARD

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The United States is the only developed country that does not have target controlled infusion devices. Why? The answer is that for many years the development of such devices was blocked by a combination of arcane regulatory issues (Is it a drug? Is it a device?) and a combination of ignorance and malfeasance on the part of the Food and Drug Administration.

I have great respect for the FDA. I have worked with the agency on many issues relating to anesthesia drugs and devices. Nearly all of the individuals associated with the

FDA are dedicated to improving public health through advances in science and technology. Nearly all...

In the area of target controlled infusions, a single individual with the Anesthesia Devices branch of the Center for Devices and Radiological Health adamantly blocked development of these devices for more than a decade. This was compounded by a profoundly ignorant pharmacokinetic analysis conducted by a physician at the Center for Drug Evaluation and Research. This analysis concluded that TCI devices had the ability to profoundly increase the variability in concentration when compared to other types of infusions. As a reviewer, I responded with a mathematical proof that this was not possible. The individual never acknowledged that my proof was correct, but it was published in *Anesthesiology* several years later.

These two individuals created a poisoned environment for all efforts to develop TCI. Graseby submitted an application to market the Diprifusor in October 1995. The application went through a number of bizarre twists. The strangest was the FDA's insistence in January 1997 that the device indicate a range rather than a number! In March 1998, 14 months later the FDA agreed that a target rather than a range was acceptable. The application then spent 4 years in limbo at the FDA, with constantly changing review teams. It was finally withdrawn in 2002, SEVEN years after submission.

In 2004 the individual who had worked so diligently to block development of TCI at the FDA was removed from his position after numerous complaints from the device industry about his bizarre behavior. The physician at CDER who performed the horrific PK analysis of TCI has long since retired from the agency. Additionally, the FDA has created an "Office of Combination Products" that specifically addresses drug-device combinations. Most critically, this office is headed by a very capable individual whose interest is not in defending the past, but in advancing the practice of medicine. These developments make it possible, and perhaps even probable, that a company that is willing to invest the time to deal with the paperwork will find a receptive audience at the agency.

OPTIMIZING HUMAN COMPUTER INTERACTION (HCI) IN ANESTHESIA CARE

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Computer driven care and patient record systems in Anesthetic care are designed to allow physicians to directly enter patient data, findings, and notes into a

computer system that may be linked to hospital-wide databases and employ decision support systems. The objectives of implementing such systems include replacing manual drug administration and hand-written paper-based records to improve access to information and the reliability of health care decision-making. However, use of these systems may also affect, in unanticipated ways, fundamental cognitive processes as well as the safety of care, involved in health care.

In this paper, we examine the effects of advanced human computer interaction (HCI) systems on physician knowledge organization, reasoning and practice. Although computerized care systems (CCS) are likely to cause changes in the nature of medical practice and are increasingly being used in medical practice, the deployment of such CCS technologies has often proved more difficult than anticipated. In some health care settings, the introduction of CCS has been fraught with difficulties, ranging from technical problems in integrating these systems with other information resources, to fundamental problems with user interfaces.

We generally consider effects of technology at several levels, from examination of individual cognitive processes to analysis of systems, where effects are considered in the context of distributed cognition (e.g., the effects of the use of systems on decision making in clinical settings). The research framework typically involves both laboratory and naturalistic study of systems, and builds on models and conceptual frameworks for understanding human-computer interaction that considers both the individual computer user and distributed aspects of cognition. A variety of methods are employed from cognitive science to characterize the skill, reasoning, and problems of subjects of varying levels of expertise as they learn to use and master information using CCS in their patient management.

A fundamental problem in medical cognition is the retrieval of information from memory. For information to be successfully retrieved, it must be organized to facilitate recovery. Some studies have shown for example, that aspects of hand-written paper records (including certain types of perceptual and visual cues) that greatly enhance decision-making may be lacking in CCS's. After having some exposure to the CCS, physicians showed at least a temporary residual learning effect. Paper-based records made after physicians' exposure to the CCS closely resembled the computer-based records in their format and organization. This is an example of the effects of technology, in which experience in the use of a technology changes users' reasoning and representation patterns, even in the absence of the technology. Since reasoning is intimately related to the organization of knowledge structures, one

can infer that the consistent use of a CCS has a direct effect on knowledge organization and reasoning patterns in medical decision-making and patient management.

Different technologies may affect users in different ways; however, it is essential that we examine and understand the dynamic nature of the interaction between physician and computer if we are to improve computer systems in health care. It is essential that the subtle yet potentially profound effects of such systems on fundamental cognitive processes be better understood, particularly as such systems are used increasingly in the making of complex and critical decisions in the operating room. It is a question of not only how the technology shapes our minds but also how our knowledge about cognition should shape technology. Organized knowledge is fundamental to the development of reasoning and decision making associated with expertise. Such an approach is warranted because some of the most enduring effects of computer technology may be both complex and unanticipated by both designers and evaluators of systems.

Whether the effects of such systems are positive or negative, it is essential that attempts be made to assess and characterize these effects. If the effects of computer systems (including CCSs) used in daily practice on human cognition can be documented and understood, the potential for using this knowledge in the design of future systems is enormous. This will help both to improve the human computer interaction and to develop systems to promote systems that reinforce safe behaviors and reasoning patterns. The design of HCI systems should take into account the dynamic nature of human-computer interaction. It should also be understood that as we update the technology with new designs, human cognition and perhaps anesthesia management will also change.

INTERINDIVIDUAL VARIABILITY IN ANAESTHETIC PHARMACOLOGY

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The variability in the dose-response relationship of anesthetic agents between subjects is huge. To get an understanding of its magnitude, examples of the pharmacokinetic-pharmacodynamic variability of midazolam, spinal bupivacaine and various opioids will be evaluated. The origin in the pharmacokinetic variability lies in the varying distribution and clearance of the agents used. These are related to changes in flow affected by age, comedication or disease state as well as by changes in hepatic function. The origin in the pharmacodynamic variability lies in the varying

response of a drug at its receptor. This response may be inherently different between subjects because of genetic factors or due to “classical” factors such as organ function, co-medication or underlying disease.^{1;2}

Genetic factors may influence both the pharmacokinetics and dynamics of anaesthetic agents. Many genetic influences on opioid effects are due to changes in the pharmacokinetics. These are described as consequences of polymorphism that affect e.g. the function of membrane transporters, the bioavailability, CNS distribution and/or elimination of the opioid. Also polymorphism of enzyme systems may affect the clearance of anaesthetic agents in many ways.

Next to these pharmacogenetic changes in pharmacokinetics, pharmacogenetic changes exist that affect purely the pharmacodynamics of anaesthetic agents. Among the effector sites of the anaesthetic agents, the best studied receptor in this research area is the μ -opioid receptor. Various mutations are reported in the μ -opioid receptor related to the exonic organization of the OPRM1 gene at chromosome 6. Mutations in the OPRM1 gene result in amino-acid exchanges in the receptor protein and thereby in changes in receptor function. SNP (single nucleotide polymorphism) 118A>G results in an amino acid exchange from asparagine to aspartate at N40D mutant receptors. This mutation naturally exists in an allelic frequency of 10-19%. Carriers of this mutation need more alfentanil for postoperative pain relief, need more morphine for cancer pain relief,^{3;4} exhibit a decreased miotic potency for M6G and morphine and an increased demand for M6G to produce analgesia. Lastly some suggest that the SNP 118A>G may be protective against opioid side effects. Not only has the μ -opioid receptor been the subject of pharmacogenetic studies. Single nucleotide polymorphism in the GABA-receptor system as coded on chromosome 4, have been associated with alcohol dependence, various types of epilepsy and a reduced effect of benzodiazepines.

Gender and ethnicity also are partially responsible for the PD-variability. Examples of these are the following. Men need more morphine for adequate postoperative pain relief, and morphine was noticed to displace the CO₂-response curve in contrast to men. Nalbuphine, has greater effect in women than in men. Also women have been noticed to emerge from propofol anaesthesia faster than men.^{5;6} Compared to Caucasians, Northern American citizens experience less respiratory depression to morphine, and Caucasians do need more morphine for analgesia than do Africans or Asians.⁷ Apart from PD-variability a varying nociception in between ethnic groups may also play a role in this.

Lastly also age and co-medication, the more classical factors regarding PK-PD variability, affect the response to anaesthetic agents. With age the propofol

requirements decrease.⁸ Also for remifentanil the EC₅₀ has been shown to decrease, and the blood-brain equilibration half-life to increase, with age.⁹ Co medication strongly affects the pharmacodynamics of both hypnotic and analgesic agents. The interaction between hypnotics generally is additive whereas that between hypnotics and analgesics appears to be synergistic.^{10;11}

In conclusion, the pharmacokinetic-pharmacodynamic variability of anaesthetic agents is huge. The main factors involved are pharmacogenetic variability as exhibited through single nucleotide polymorphism, effects of gender and ethnicity, as well as the more "classical" factors as organ function, co-medication or underlying disease.

References:

1. Lotsch J, Geisslinger G: Are mu-opioid receptor polymorphisms important for clinical opioid therapy? *Trends in Molecular Medicine* 2005; 11: 82-9
2. Lotsch J, Skarke C, Liefhold J, Geisslinger G: Genetic predictors of the clinical response to opioid analgesics - Clinical utility and future perspectives. *Clinical Pharmacokinetics* 2004; 43: 983-1013
3. Klepstad P, Dale O, Skorpen F, Borchgrevink PC, Kaasa S: Genetic variability and clinical efficacy of morphine. *Acta Anaesthesiologica Scandinavica* 2005; 49: 902-8
4. Klepstad P, Rakvag TT, Kaasa S, Holthe M, Dale O, Borchgrevink PC, Baar C, Vikan T, Krokan HE, Skorpen F: The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiologica Scandinavica* 2004; 48: 1232-9
5. Gan TJ, Glass PS, Sigl J, Sebel P, Payne F, Rosow C, Embree P: Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *Anesthesiology* 1999; 90: 1283-7
6. Hoymork SC, Raeder J, Grimsmo B, Steen PA: Bispectral index, serum drug concentrations and emergence associated with individually adjusted target-controlled infusions of remifentanil and propofol for laparoscopic surgery. *British Journal of Anaesthesia* 2003; 91: 773-80
7. Dahmani S, Dupont H, Mantz J, Desmots JM, Keita H: Predictive factors of early morphine requirements in the post-anaesthesia care unit (PACU). *British Journal of Anaesthesia* 2001; 87: 385-9
8. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90: 1502-16

9. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; 86: 10-23

10. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG: Propofol anesthesia and rational opioid selection: determination of optimal EC₅₀-EC₉₅ propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology* 1997; 87: 1549-62

11. Vuyk J: Clinical interpretation of pharmacokinetic and pharmacodynamic propofol-opioid interactions. *Acta Anaesthesiol. Belg.* 2001; 52: 445-51

REMIFENTANIL AND CARDIAC PRECONDITIONING

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Ischaemic preconditioning (IPC), which is defined as previous exposure to transient cardiac ischaemia, provides protection from subsequent myocardial infarction and arrhythmia. The phenomenon occurs in two phases: an early phase that starts within a few minutes after the initial ischaemic stimulus and lasts for 2-3 hours, and a late phase, which begins 12-24 h later and can last for up to 3-4 days. It is now well known that certain pharmacological agents can induce the same effects as ischaemic preconditioning and a number of these drugs are used in anaesthesia. This may represent a safer and more practical way of eliciting cardioprotection, particularly in the diseased myocardium and in the perioperative setting where anaesthesia mediated or facilitated cardiac preconditioning around the stressful time of surgery would be particularly beneficial in patients at high-risk for cardiac morbidity.

Opioids (OP) are widely used for the treatment of pain and have been shown to confer both the acute and delayed phase of cardioprotection via OP receptors, effects similar to IPC. It was found that both the cardiac δ -opioid (DOP) receptor (especially $\delta 1$) and κ -opioid (KOP) receptor as well as extracardiac μ -opioid (MOP) receptor are involved in opioid-induced cardioprotection. Activation of DOP and KOP leads to protein kinase C (PKC) activation. Activated PKC acts as an amplifier of the preconditioning stimulus and stabilizes, by phosphorylation, the open state of the mitochondrial KATP channel (the main end-effector in anaesthetic preconditioning) and the sarcolemmal KATP

channel. The opening of KATP channels ultimately elicits cytoprotection by decreasing cytosolic and mitochondrial Ca²⁺ overload. Volatile anaesthetics can also elicit acute pharmacological preconditioning; however, they do not consistently produce a second window of protection 24 h after administration in animal studies.

Remifentanyl is a potent, ultra-short-acting phenylpiperidine opioid with a rapid onset, which is often used in high doses during anaesthesia and is a suitable replacement for nitrous oxide. It has no direct myocardial depressant effects yet facilitates rapid recovery which makes it attractive as a practical preconditioning agent. Ligand binding affinity studies show that remifentanyl has a high affinity for the MOP receptor (EC₅₀ = 2.6 nm) with a relatively lower affinity for the DOP receptor (EC₅₀ = 66 nm) and KOP receptor (EC₅₀ = 6.1 μm). Previous studies in our laboratory have demonstrated that remifentanyl preconditioning confers acute cardioprotection in the intact rat heart, and the effect is mediated via cardiac KOP and DOP and extracardiac MOP receptors – remote preconditioning. More recently we have shown that remifentanyl also produced delayed cardioprotection in a dose dependent manner in anesthetized rats 12 to 36 hours after administration.

Although these modulatory effects on KATP channels have been investigated almost exclusively in laboratory investigations, they may have potential implications in clinical medicine. Important questions regarding the clinical utility and applicability of perioperative cardiac preconditioning remain unresolved and need more experimental work and randomized controlled clinical trials. It is well recognized that coronary artery bypass surgery requiring cardiopulmonary bypass results in myocardial injury as detected by markers of myocyte damage. The mechanism of the injury is multifactorial, but includes ischaemia during cardioplegia induced cardiac arrest and the systemic inflammatory response associated with cardiopulmonary bypass. Opioids have been used in cardiac surgery for years in attempt to reduce stress and we have clinical studies on going in this field.

References:

1. Remifentanyl preconditioning confers cardioprotection via cardiac kappa- and delta-opioid receptors. Zhang Y, Irwin MG, Wong TM, Chen M, Cao CM *Anesthesiology*. 2005; 102: 371-8.
2. Remifentanyl preconditioning protects against ischemic injury in the intact rat heart. Zhang Y, Irwin MG, Wong TM. *Anesthesiology* 2004; 4:918-23. Vane JR.. Inhibition of Prostaglandin synthesis as a mechanism of action for aspirin like drugs. *Nature*. 1971; 231:232-5.

3. Remifentanyl mimics the cardioprotective effect of ischemic preconditioning via protein kinase C activation in open chest rats. Zhang Y, Irwin MG, Wong TM et al. *Acta Pharmacologica Sinica* 2005; 26: 546-550.

4. Remifentanyl preconditioning confers delayed cardioprotection in the rat. Li YH, Yu CK Wong GTC, Wong TM, Irwin MG. *British Journal of Anaesthesia*. In press.

DEXMEDETOMIDINE

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The alpha₂-adrenoceptor agonist dexmedetomidine was originally developed as a sedative and analgesic agent for use in intensive care [1]. However, it has a number of unique pharmacodynamic properties which also make it useful in anaesthesia – decrease in MAC, analgesia without respiratory depression and a significant reduction in catecholamine secretion [2]. This drug heralds an exciting new chapter in the practice of anaesthesia. Dexmedetomidine has high alpha₂ selectivity compared to clonidine and has been the subject of numerous clinical studies in the past decade. Attributed benefits are both direct, such as sympatholysis, and indirect from its anaesthetic and analgesic effects. Three types of alpha₂-adrenergic receptors are found in the human body. These receptors have been designated alpha_{2A}, alpha_{2B} and alpha_{2C}. With advances in molecular medicine and gene cloning techniques, the genes for all these 3 receptor subtypes have been cloned. The genes for subtype 2A, 2B and 2C are located on chromosomes 10, 2 and 4 respectively. Therefore, these receptor subtypes are also currently named alpha_{2-C10}, alpha_{2-C2} and alpha_{2-C4}. Alpha₂-adrenergic receptors are found in coronary arteries, presynaptic nerve endings, liver, pancreas, spleen, kidney and the brain. The activation of these receptors leads to various effects such as vasoconstriction and vasodilatation, glycogenolysis and gluconeogenesis, decreased insulin secretion and sedation and analgesia. These receptor subtypes have a characteristic distribution in the human body, which suggests distinct physiological roles for each of them. Alpha_{2A} is found throughout the brain, but most abundantly in the locus coeruleus. It is also found in abundance in the lung, the spleen, the pancreas and aorta. Alpha_{2B} is found in the thalamus, as well as in the heart, aorta, the spleen and the liver. Alpha_{2C} is found in the basal ganglia and in the aorta, the heart, the spleen and is particularly abundant in the kidney. Because agonists or antagonists that are highly selective for each of these subtypes are currently not available, the exact physiological role of

each receptor subtype remains to be elucidated. We have found dexmedetomidine particularly useful because of its non-gabaminergic sedation mediated via the locus coeruleus. This induces electroencephalographic activity similar to natural sleep thereby allowing facilitated arousal and avoiding patient disorientation and facilitating cooperation. Thus it is particularly useful in operations such as endovascular procedures and carotid endarterectomy under regional anaesthesia. The drug also reduces catecholamine secretion, thereby reducing stress and leading to a modest (10-20%) reduction in heart rate and blood pressure, which may be particularly beneficial in patients with cardiovascular disease. We have also found that the drug can be reliably administered intranasally and, as such, may have a useful role in premedication.

References:

1. Dexmedetomidine: handbook of clinical applications. Irwin MG, Wong GTC. Lippincott Williams & Wilkins ISBN 0781771358. 2006.
2. A double blind crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee HY. Anaesthesia and Analgesia. In press.
3. A comparison of dexmedetomidine and midazolam for sedation during wisdom teeth extraction. Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng JKF, Irwin MG. Anaesthesia. In press.

PATIENT CONTROLLED SEDATION TECHNIQUES

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Introduction:

The use of locoregional anaesthesia for a variety of surgical procedures is increasing as it provides not only satisfactory operating conditions and good intra and post operative analgesia, but also has advantages in terms of health economics. Also some surgical procedures which in the past have required general anaesthesia and open operation can now be carried out per-cutaneously under local anaesthesia. In order to improve patient acceptability, comfort and reduce stress, it is common practice to provide some form of sedation during such procedures. Ideally during sedation, the patient should be relaxed, comfortable and co-operative throughout the procedure. In practice, achieving this ideal may be the most challenging aspect of anaesthesia.

Sedative Agents:

An ideal sedative agent should produce a rapid and smooth onset of action and allow easy control of the level and duration of sedation. It must have rapid offset and recovery without rebound or emergence effects to enable rapid discharge from the recovery area and hospital. Of the currently available drugs in Europe propofol and midazolam are the two most suitable agents with midazolam being particularly popular with non-anaesthetists. However, the pharmacokinetics properties and recovery characteristics of propofol make it potentially better suited for short-term sedation.

Although both drugs achieve a rapid peak blood concentration after a bolus dose, there is considerable delay to peak clinical effect with midazolam compared to propofol. In practice this means there is more potential for dose stacking and eventual overdose with midazolam, this is supported by available studies comparing the 2 drugs (1). Remifentanyl is an opioid with a rapid onset and off set and numerous studies have described its use by infusion as a sedative agent alone or in combination with hypnotic agents during procedures associated with noxious stimulation. It must be remembered that remifentanyl in common with all opioids is a powerful respiratory depressant and this is particularly true when combined with hypnotic agents. Therefore remifentanyl as a single agent or as an adjuvant in sedative techniques must be used with caution to avoid loss of airway and profound respiratory depression. Dexmedetomidine the Alpha 2-adrenoceptor agonist is an interesting agent, it has little effect on respiration at sedative doses and also possesses analgesic properties (2). Unfortunately it is currently not licensed for use in Europe

TCI for sedation:

The problem with propofol particularly for the non-anaesthetist is its short duration of action requiring repeated bolus dosing or complex infusion regimens. An alternative approach to the delivery of this drug is the use a target controlled infusion (TCI) as pioneered by Kenny and colleagues (3). TCI uses a pharmacokinetic model of propofol to provide an infusion profile designed to achieve and maintain any select target blood concentration. In this way the physician can easily titrate the target blood concentration up or down in order to achieve the desired level of sedation. Skipsey and colleagues used TCI to provide sedation for orthopaedic procedures under spinal anaesthesia (4). They concluded that the system provided good quality sedation with the patients remaining within the target sedation score range 87% of the time with little over sedation. The median target concentration for this group was 0.9 µg/ml with a range of 0.15- 2.6 µg/ml. Church and co-workers used TCI infusions for sedation in patients undergoing gastroscopy. In this study an initial target of 1.5 µg/ml was selected and increased by 0.5

µg/ml increments every 30 seconds until the patient's speech became slurred. The median target concentration of propofol in the group was 2.5 µg/ml with a range of 1.5- 4 µg/ml (4). The higher targets required in the later group are explained by the increased level of surgical stimulation in this group. As can be seen from the range of target values in these 2 studies there is considerable intra-individual variation in propofol requirements, thus it is not possible to predict in advance the target blood or effect site concentration any patient will require for adequate sedation. It is therefore necessary to titrate the TCI blood concentration to the desired effect in the patient. Although TCI allows rapid titration of the blood concentration of propofol, the clinical effect of the drug is delayed, and can be represented by a theoretical effect site concentration. Thus the physician needs to be aware of this delay in order to avoid potential overdosing by increasing the target concentration before the effect site concentration has had time to equilibrate.

Patient controlled sedation:

A number of researchers have allowed patients to self-administer sedative drugs Patient Controlled Sedation (PCS), in a manner analogous to patient controlled analgesia; this appears to be strongly preferred by patients (6). The technique involves the patient self-administering a sedative agent to the point at which they are satisfied with the level of sedation. Such an approach has the potential to overcome the inter-individual pharmacodynamic variation. PCS appears to be safe and acceptable to patients, surgeons and anaesthetists. Over the past decade more than 30 studies of patient controlled sedation have been published. Two methods of administration of sedative agents for PCS have been used. Most studies describe the use of a modified Patient Controlled Analgesia (PCA) pump which delivers a set amount of bolus sedative agent with or without a lockout time. More recent studies have describe the use of a modified TCI device with the patient being able to increase the target concentration for sedation by pressing the demand button.

All studies in this field describe satisfactory results with PCS and report a high degree of patient satisfaction. However, all studies involved supervision by an anaesthetist and few studies have reported any objectively measurable benefits. Osborne argues that careful monitoring by the anaesthetist is mandatory and the use of monitored PCS substantially increases the anaesthetist responsibility (7). This begs the question; does monitored PCS represent an improvement over anaesthetist controlled sedation and can the delivery system be made safe enough to be used without anaesthetist supervision? Kenny and colleagues have developed a system which allows patients to operate a Target Controlled Infusion of propofol to provide

sedation to themselves. This PCS technique referred to as Patient Maintained Sedation (PMS), combines the benefits of Target Controlled Infusion (TCI) with patient controlled feed back to produce safe intra operative sedation (8). In this study, 36 un-premedicated patients, undergoing surgery under regional anaesthesia, were recruited. An intravenous Propofol infusion was started at a target plasma level of 1.0 µg/ml. The patient was then able to increase the target propofol concentration in 0.2 µg/ml increments by pressing a demand button. There was a lockout interval of 2 minutes and a maximum permissible target concentration of 3 µg/ml. The patient was then given control of the handset and was able to increase the propofol target concentration in 0.2 µg/ml increments by pushing twice within 1 second on a demand button. For the first 20 minutes of use if there were no demands made in any 6 minute period the system decreased the concentration by 0.2 µg/ml, there after it decreased after 12 minutes without demand and every 12 minutes thereafter until the baseline target concentration of 0.2 µg/ml was reached. In the study optimum sedation was provided at median target concentration of 0.8 - 0.9 µg/ml. The investigators observed that there was no cardiovascular instability and little over-sedation. Respiratory rate decreased with the onset of sedation and the lowest recorded rate was 10 breaths/ minute. There were no instances of airway obstruction requiring intervention. However, 8 patients required supplementary nasal oxygen therapy because of oxygen saturation readings below 92% and oxygen supplementation improved the saturation in all cases. Recovery was rapid following the cessation of the infusion and there were no delays in discharge from recovery room. This technique combines the benefits of TCI with patient controlled feedback and produces safe intra operative sedation during loco-regional anaesthesia with rapid recovery and high patient satisfaction.

Some potential difficulties with PCS have been raised, including the question of whether patients can adequately judge their sedation needs while already sedated. The clinical experience obtained to date, however suggests that this technique is effective and highly acceptable to patients. It accommodates wide variations in sedation requirements between patients and allows patients to receive the level of sedation that they want. Patients also derive psychological benefit from this method of control by being able to modify anticipated unpleasant stimuli.

Effect site controlled PMS:

It may be appreciated from the above that the sedative effect of propofol is related more closely to the calculated effect site concentration than the blood concentration. It would therefore be preferable to target the effect site rather than the blood concentration with a TCI system. The technology to do this is available but

not currently regulatory approved. Figure 2 shows a comparison of effect site and blood targeted TCI. The effect site system allows the effect site to rise to its target value more rapidly without the risk of overshoot. Such a system with patient control added would allow patients to achieve a given level of sedation more rapidly with a shorter lockout period with little risk of over-sedation. We have used effect site targeted TCI with patient control to provide self administered sedation to volunteers (8). The system was set with an increment of 0.1 µg/ml and a lockout time of 1 minute. Volunteers were asked to try to anaesthetise themselves with the system. No subject lost their airway or de-saturated below 90 % although all patients were given supplementary oxygen via a nasal cannula. This new method of delivery has the potential to be the most effective safe and responsive method of sedation and requires further study.

Summary:

Propofol is a safe and effective alternative to midazolam for providing conscious sedation. The use of TCI facilitates the delivery of propofol and provides effective titration of sedation. Patient controlled sedation using propofol provides many benefits and gives a high degree of patient satisfaction. The combination of patient control TCI and effect site controlled TCI offer exciting new prospects for conscious sedation and warrant further investigation.

References:

(1) Pac-soo et al “Patient controlled sedation for cataract surgery using peribulbar block” *British Journal of Anaesthesia* 1996, 77(3) 370-374.

(2) Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992;77:1125-1133.

(3) White, M. and Kenny, G.N. (1990) Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 45, 204-209.

(4) Skipsey IG, Colvin JR Kenny GN Sedation with propofol during surgery under regional blockade (1991) *Anaesthesia* 48:210-213, 1993.

(5) Church JA, Stanton PD, Kenny GN & Anderson JR. *Gastrointest.Endosc.* 37:175-179, 1991.

(6). Rudkin et al “ Intra-operative patient controlled sedation” *Anaesthesia* 1992, 47:376-81.

(7). G A Osborne et al “ Monitored patient controlled sedation: Practical technique or academic research tool” *European Journal of Anaesthesia* 1996,13,Suppl, 13:13-17.

(8). Irwin et al “Patient maintained propofol anaesthesia” *Anaesthesia* 1997,52,(6)525-30.

(9) Absalom AR, Sutcliffe N. Effect-site targeted patient-maintained sedation with propofol. *Anesthesiology* 2000; 93,Suppl.: A291552.

SAFETY, DRUGS AND MONITORING IN REMOTE PAEDIATRIC SEDATION

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Non operating room anaesthesia and sedation performed in paediatric patients have seen in the last decade an explosive growth.

The shift from the usual “scenario” of the operating theatre to “remote” locations is driven by cost saving politics and convenience for patients and providers (Lester, *Curr Opin Anaesth*, 1998).

This is particularly true in paediatric patients who suffer the consequences of the separation from the familiar environment.

Furthermore the number of diagnostic and therapeutic procedures, performed on children is widely increased and more attention is given to the relief of pain and anxiety in this category of patients. Physical restraint is not accepted anymore (Zeltzer, *Pediatr Clin North Am*, 1989) according to several studies demonstrating emotional reactions to pain and stress even in premature babies. (Anand, *Prog Food Nutr Sci*, 1986; Weisman, *Arch Ped Adolesc Med*, 1998). In fact they can react to pain with negative short and long term effects as intraventricular haemorrhage and decreased pain threshold.

Avoiding the classical general anaesthesia doesn’t leave out of consideration a particular care underlined from recently issued standards and guidelines published by international associations as ASA, JCHAO, APA (AAP, *Pediatrics*, 1992; American College of Emergency Physicians: *Guidelines for paediatric sedation*, 1995)

The anaesthesiologist has to move to several locations: Neonatal Intensive Care Unit (NICU); Dentistry, Radiology, Emergency Department; Oncology Ward, Ophthalmology and Endoscopy ambulatories.

As observed by Cravero and Blike (Cravero and Blike, *Curr Opin Anaesthesiol*, 2006): “..the current state of pediatric sedation reflects the tension between the need for high-quality pediatric sedation and the lack of qualified personnel to deliver this care..”. In fact very often there are sedation studies performed by specialists

other than anesthesiologists who publish their experience with sedation outside operating room (OR) more than anesthesiologists do (Vardi, Crit Care Med, 2002).

These providers have published many papers under the title of “sedation” when they are clearly describing “anaesthesia”. This issue is serious since delivery of paediatric anaesthesia/sedation care outside the OR is an example of a high-risk, low-error-tolerance setting for anaesthesia services

However there is a problem concerning the definition of sedation in children as opposed to adults: the Royal College of Anaesthetists has defined a state of conscious sedation which is “depression of nervous system during which verbal contact is maintained”. Sedation deeper than this, is an unconscious state which is considered to be equivalent to anaesthesia. Maintaining “verbal contact” is very safe but it is only useful in cooperative patients, and children usually are not included in this category. Sedation often requires to arouse the sleeping child if necessary, but this is impractical if the procedure needs immobility. Because of that, conscious sedation is not possible for the most part of small children during magnetic resonance imaging (MRI).

The American Academy of Pediatrics has defined deep sedation as a state deeper than conscious sedation but not as anaesthesia (AAP Committee on Drugs, Pediatrics 2002). Anyway, whatever the depth, sleep must be safe and it has been suggested a particular definition of deep sedation in children as: “a technique in which the use of a drug produces a state of depression of the nervous system such that the patient is not easily aroused but which has a safety margin that renders the loss of airway and breathing reflexes unlikely”.

Concerning all these considerations it is out of doubt the advantage of a dedicated anaesthesiologist, because the safety and success of sedation depends almost entirely on the use of protocols and on the staff who administer them. In fact a continuous control is required and sedation has to be tailored on the child particularly on his age, medical condition (current medications, fasting status, disease processes) and on the type and length of procedure.

There are procedures such as colonoscopy, bone marrow aspiration or dental restoration that require analgesia and procedures such as magnetic resonance imaging that are painless but require a motionless patient.

In order to better understand the nature and frequency of adverse events in paediatric sedation outside the OR it has been created by Cravero et al a Paediatric Sedation Research Consortium including more than 30 institutions in the US and Canada that share data on paediatric sedation activity and on more than 50.000 sedations delivered by anaesthesiologists and other

providers. This Consortium is addressed to identify the demographics of patients, procedures, techniques, outcomes and adverse events (Cravero, Pediatrics, 2006). Fortunately it has been found that serious adverse events in these kind of procedural sedations are rare reporting no deaths, only one cardiac arrest and one aspiration. Unanticipated admission to the hospital occurred approximately once every 1500 sedations; vomiting once every 200 procedures; stridor, laryngospasm, wheezing or apnoea once every 400 procedures and airway and ventilation interventions once every 200 sedations.

This Consortium allowed also to highlight special topics such as:

- age less than 3 months as a predictor of adverse events;
- ASA status more than 3 associated with a higher rate of airway complications;
- nature and number of complications related to the different sedation providers;
- the number of events related to the drugs used;

As the typical paediatric patient needing anaesthesia for diagnostic and therapeutic procedures has a high rate of recidivism, every effort must be made to minimize fear and anxiety with each procedure in the course of the illness. In fact many of these patients have complex illness with treatment programs lasting months or years.

As reported by JCAHO it is useful to recreate a virtual operating room environment by using microsystems for NORA procedures providing the same standards to every patient regardless of locations. AAP has established standards for children receiving non operating room sedation.

Usually there should be no limitation in this context about drugs options, but inhaled anaesthetics should be avoided in absence of sufficient space for anaesthesia machines or scavenger systems. So it becomes evident that TIVA should be the best choice. However it should be underlined that intravenous drugs as pentobarbital, propofol, ketamine advocated for sedation by non-anaesthesiologists would be selected by anaesthesiologists as general anaesthetics and should require a specific experience to administer them.

Among these, propofol continues to be the most utilized drug because of its pharmacological profile of rapid induction, rapid clearance and few airway complications. In a survey on oncology patients propofol sedation performed on the ward was preferred to general anaesthesia in the operating room (Van Heijne, Paed Anaesth 2004).

Furthermore propofol does not develop tachyphylaxis even after 5 or 6 weeks of daily treatments (Keidan,

Anesthesiology, 2004). Despite its high safety profile propofol can depress respiration and it shows a Bispectral Index (BIS) value of about 30 related more to general anaesthesia than simply to sedation (Reeves, Pediatrics, 2004).

Midazolam can be safely administered to children for premedication and sedation by several routes (oral, nasal, rectal, intravenous) but it is more effective when associated with other sedatives. Combined with propofol may allow the separation from parents, greater patient's comfort and the reduction of propofol dose because of the synergic action.

Ketamine administered in low dose (0.5 mg/kg) at the beginning of the procedure has been reported to reduce propofol infusion and consequently the respiratory depression (Tomatir, Pediatric Anaesth, 2004). Ketamine has gained popularity again in the last years particularly for children and outside the OR thanks to its ability to induce anaesthesia by a variety of routes, including orally and intramuscularly, when intravenous access is not available. It is also able to maintain respiratory rate and haemodynamic stability.

Dexmedetomidine, alfa2 agonist, is a new sedative drug that has not been widely tested in children. It seems to induce bradycardia and hypotension. Few reports in paediatric literature indicate inadequate sedation and the conversion to general anaesthesia (Fahy, Anaesth Intens Care, 2004). Further studies are required to establish the real utility of this drug in children.

In our experience different associations of these drugs allow us to obtain different degree of sedation in relation to the specific procedure.

In NICU we utilize midazolam/remifentanil or propofol/remifentanil to provide deep sedation and anaesthesia to intubated premature babies undergoing lasertherapy for retinopathy of prematurity.

In Oncology Ward propofol infusion combined with ketamine or alfentanil provides to smaller children a deep sedation for bone marrow aspiration, lumbar puncture and CVC positioning, whereas midazolam and remifentanil bolus provide conscious analgo-sedation to older children.

In Nuclear Medicine Ward propofol infusion alone in high doses (10-30 mg/kg/hr) shows great efficacy for neonates and children undergoing SPECT.

Propofol infusion is also useful for electroretinogram or bulbar ecography in Ophthalmology Ambulatories.

Propofol/remifentanil is the best choice in children and handicapped patients undergoing dental restoration in Dentistry Ambulatories when general anaesthesia is required and no scavenger systems are available.

Providing anaesthesia care outside the OR requires attention to the same requirements for safe patient care as are followed in the operating room. (ASA, Guidelines for non operating room anesthetizing location, 2003).

For these reasons particular attention is addressed to all the new monitoring methods much more sophisticated than in the past. Although standard guidelines include oxygen saturation this monitoring is limited as a guide to respiratory function and does not measure ventilation. Recently a new monitoring technique has been introduced. Capnography via an EtCO₂ monitor measures

carbon-dioxide concentration during ventilation and aids the clinician to identify hypoventilation and apnoea in the sedated patient at an earlier stage than conventional monitoring. The new microstream devices have a room-sampling very small working efficiently also with very low ventilatory flows as in neonatal patients in spontaneous ventilation. The graphic representation of EtCO₂ improves the detection of alveolar hypoventilation and allow early detection of arteriolar oxygen desaturation during sedation. In fact Vargo reported 57% episodes of apnoea detected by capnography and not by standard monitoring (Vargo, Gastrointest Endosc, 2002) and Lightdale (Pediatrics, 2006) supports capnograms, rather than absolute EtCO₂ values, as the most sensitive measure of ventilation in not-intubated patients.

BIS monitor is another device that can be useful during procedural sedation and during general anaesthesia. It is able to objectively measure the depth of sedation by analyzing EEG signals through a cutaneous probe.

It enables the physician to titrate sedative medications to a desired effect and thereby reduces the risk associated with over-sedation.

Concerning recovery and discharge, with exception of large children's hospitals, most institutions do not have recovery areas with adequate paediatric nursing staff and the anaesthesiologists are responsible for emergence and discharge of children sedated outside the OR. Furthermore infrastructures as recovery areas with room for parents and discharge instructions about oral fluids, pain and PONV management are lacking.

University of Michigan Sedation Scale (UMSS) and Modified Maintenance of Wakefulness test may be useful criteria for safe discharge.

It is out of doubt that new monitoring devices, such as Capnography and BIS, will facilitate the efficacy of procedural sedation, will improve early recognition of hypoventilation and will reduce the risk of over-sedation, enhancing the safety of an early discharge.

TCI SYSTEMS IN SEDATION AND ANALGESIA FOR ENDOSCOPIC PROCEDURES

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Introduction:

The requirements for administration of sedation and/or analgesia for minimally invasive diagnostic and therapeutic procedures have increased enormously. Anesthesia administration is not an innocuous procedure, but it is made safe because there is an anesthesiologist that knows how to control the effect of drugs and how to detect and manage any complication derived from their administration.

This presentation aims to discuss the special features of providing sedation-analgesia for digestive endoscopic procedures, with special emphasis in the possibilities of using TCI systems, to achieve an optimum degree of comfort while avoiding undesired effects.

Propofol and remifentanyl in TCI systems:

Although several drugs and ways of administration could be used to provide sedation, nowadays the most used drugs because of its effect profile are propofol and remifentanyl. For both drugs there are pharmacokinetic (PK) and pharmacodynamic (PD) models published that establish the relation between dose, plasma concentration and effect, in most of the cases, based on the effect induced on the electroencephalogram (EEG).

TCI systems are devices that take advantage of intravenous infusion pumps and the knowledge about the behaviour of a drug in the body (PKPD models), to administer exclusively the amount of drug that will cause a “defined” level of drug effect during a “defined” period of time. TCI systems have been used in research projects for more than twenty years. Different software programs have been used for this purpose like Stanpump, CACI, Stelpump, CATIA, and more recently RUGLOOP. Probably Stanpump has been the most used TCI software in research because it is the one including most information about drugs and different models including also the feature of incorporating “home made” PKPD models. In 1997 the Diprifusor was released on the market in the European Community, to allow the administration of propofol according to the model published by Marsh et al. It allowed targeting propofol in plasma, not on the effect site, and the model was scaled according to the weight of the patient. Currently different commercial devices are available: TCI Base Primea from Fresenius, Asena PK from Cardinal Health and InfusoMat from B|Braun.

PRINCIPLES OF TCI IN THE ICU

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In many anesthesia departments in Europe, target controlled infusion (TCI) of anaesthetics is already an established method of drug administration. It is currently used mainly in adults and only for selected drugs, mostly the administration of propofol and remifentanyl. TCI is based on pharmacokinetic principles. The principles should also be applicable for other patient populations and other environments.

There are many differences between treating a patient in the intensive care unit (ICU) and during anaesthesia but with regard to the pharmacokinetic principles there are no clear differences. In the context of this lecture we will primarily focus on TCI of anaesthetics in the ICU. It goes without saying that theoretically also the administration of other classes of drugs could profit from more sophisticated pharmacokinetic based methods.

Usually the duration of drug therapy (sedation, analgesia) is longer in ICU. Patients are normally less frequently exposed to painful stimulation compared to during surgery. ICU patients also have concomitant diseases and treatments which can impact the pharmacokinetics of the anaesthetics. On the other hand there are no differences between the patients during anaesthesia and in ICU with regard to pharmacokinetic and pharmacodynamic variability and the pharmacokinetic and pharmacodynamic principles are the same. First we will review the principle of model based drug administration.

When anaesthetics are administered they should always be dosed based on some idea regarding the desired effect. For this purpose at some point some device (syringe pump, vaporizer) has to be manipulated. In traditional modes of i.v. drug administration this is an infusion rate. There is unfortunately no clear and unique relationship between the infusion rate and a concentration. Only if the infusion rate is held constant for a rather long time will it correspond with a defined concentration – the steady state concentration. In addition it takes time until the drug has penetrated into the site of drug effect. Often we want to reach the effect associated with a “pump setting” as fast as possible. Then the “effect site concentration” must be the “target”.¹ It is not possible to measure this effect site concentration, it can only be estimated based on pharmacokinetic models which were developed in studies where drug concentrations and effect data has been measured simultaneously.²

Simulations show that the effect site concentration follows the change infusion rate very slowly. The association between the infusion rate and the effect site concentration (i.e. the effect) is very weak. With pharmacokinetic model based computer controlled infusion systems the target (and the setting at the infusion device) will be the effect site concentration. The system will calculate changing infusion rates which will deliver very different amounts of drug over time than the constant infusion would do.

A challenge for TCI in ICU are differences the pharmacokinetic behaviour of severely ill patients. Furthermore therapies such as haemodialysis will alter the pharmacokinetics of drugs. Although, e.g. remifentanyl pharmacokinetics is not very much altered in patients with renal insufficiency or other organ dysfunction,³ distribution and elimination of other drugs will be altered in these patients. Therefore there would be bigger differences between predicted and measured drug concentrations. With the traditional model of administration the infusion rate would be reduced in these patients according to the observed effect. Similarly in TCI mode the target concentration has to be reduced.

Although it could be useful to adjust the pharmacokinetic models for ICU patients in special situations it could increase the complexity of the technology with no clear advantage.

Despite some shortcoming of TCI in some situations it must be noted that model based drug administration (TCI) is never worse than the traditional modes of administration, but in most situations better.

References:

1. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer- controlled infusion pump. 1992; 20: 147-169
2. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. 1979; 25: 358-371
3. Dershwitz M, Rosow CE: The pharmacokinetics and pharmacodynamics of remifentanyl in volunteers with severe hepatic or renal dysfunction. *Journal of Clinical Anesthesia* 1996; 8: 88S-90S

EVALUATING ANALGOSEDATION IN ICU

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Introduction:

“The intensive care of consciousness is as important as the intensive care of all other organ systems”. By saying these words at the ESA congress held in Paris in 2004, Ramsay(1) confirmed the importance of analgo-sedation for all the patients hospitalized in Intensive Care Unit. As everybody knows Ramsay is “the Father “ of the scoring system for sedation level monitoring. The Ramsay sedation score is the most commonly used in ICU.

Until 30 years ago, when Ramsay thought about his sedation score, there weren't specific systems for monitoring analgo-sedation. So, many drugs were given just “in case of need”. It was easy to have under or over-sedation. Patients' stress and pain in intensive care unit must be avoided . It's really important to have for our patients an “analgesia based sedation”

But nowadays there isn't a common consent about the consciousness sedation level (which is the standard sedation level we have to reach?)(2). Moreover there aren't common sedation protocols. Controlling pain and stress in ICU is not considered one of the most important target, even more if we are in front of bad patient from an aemodynamic point of view (1)

The right sedation level is different in each patient, according to their own clinical characteristics (3,4). Nowadays there isn't a common consent about which drugs and which doses must be used, so sedation monitoring becomes a very hard task because there isn't any “perfect instrument“ representing an “international gold standard” scientifically validated for this specific aim (5).

Analgo-sedation monitoring remains one of the most important target for critical patient's management to obtain the right sedation level: Sedation quality = (right sedation hours / total sedation hours) X100 (6)

Sedation quality > 85% . To reach a good sedation quality is an important target in order to avoid under or over-sedation (2,7)

As a matter of fact many methods have been suggested in order to monitor sedation level: from scoring systems, representing a subjective monitoring way, up to the latest instrumental monitoring systems (objective monitoring way).The latter aren't supported by unquestionable clinical evidences, they are still object of many clinical studies.

Sedation Monitoring:

Subjective monitoring systems - the only validated methods in monitoring in ICU are the scales of sedation

level based on clinical observation and directly recorded by direct observation, giving attention to the relationship between patient and mechanical ventilation.

In scientific literature more than 30 scales have been described (8). Each of them is based on different characteristics to describe consciousness levels and agitation degree. Ramsay sedation score is the most used in daily clinical practices and studies, described by Ramsay and coll. in 1974.

The characteristics of a scoring system are (2):

- a good weighted index (agreement between several observers)
- the simplicity
- the reliability
- the exactness
- patient's lower discomfort

In 2000, in a systematic review, De Jonghe and coll. (9) analyzed 25 studies made on patients sedated in ICU. They observed the high reliability and the good correlation between different sedation scores compared with the Ramsay one and the Comfort scale; but there weren't studies confirming their "sensitivity" for smallest changes in sedation.

Here the more commonly scoring systems used in Intensive Care Unit

Ramsay Sedation Score:

The most internationally used in daily clinical practices and studies is the Ramsay sedation score, described by Ramsay and coll. in 1974 (10)

This score is often used to compare and validate new monitoring systems, both objective and subjective.

The score identifies clinical agitation or sedation. According to many experts it is not a sedation score system but a scale used to value different consciousness steps.

These consciousness steps are not clearly defined. It's the reason why Ramsay sedation score was considered too much subjective and not so good.

But on the other side, several studies tested its good reliability, with a very good weighted index. That's why Ramsay score is considered reproducible in clinical practices (9)

Glasgow Coma Scale modified by Cook and Palma

Described by Cook in 1989, it was adopted to describe the coma state in patient with politrauma.

In many ICU it's used also as a sedation monitoring system.

The scale comprises three tests: eye, motor and verbal responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), the highest is 15 (fully awake person).

- Best eye response (E)

There are 4 grades:

4. Eyes opening spontaneously.
3. Eye opening to speech. (Not to be confused with an awaking or a sleeping person; such patients receive a score of 4, not 3.)
2. Eye opening in response to pain.
1. No eye opening.

- Best motor response (M)

There are 6 grades:

6. Obeys commands. (The patient does simple things as asked.)
5. Localizes to pain
3. React from pain (pulls part of body away when pinched; normal flexion).
3. Flexion in response to pain (decorticate response).
2. Extension to pain (decerebrate response: adduction, internal rotation of shoulder, pronation of forearm).
1. No motor response.

- Best verbal response (V)

There are 5 grades:

5. Oriented (Patient responds coherently and appropriately to questions such as the patient's name and age, where they are and why, the year, month, etc.)
4. Confused (The patient responds to questions coherently but there is some disorientation and confusion)
3. Inappropriate words (Random or exclamatory articulated speech, but no conversational exchange)
2. Incomprehensible sounds (Moaning but no words)
1. None

The execution of the score causes minimum discomfort for the patient.

During the years, several studies have confirmed that this scale could be easily reproduced. It has a good weighted index, so it's a good scale both for clinical practice and clinical researches (2).

Sedation-Agitation Scale:

This score was described by Riker in 1994, and validated by the same author in ICU in 1999.

He reached a good weighted- index. But this score doesn't consider the relationship between patient and mechanical ventilation.

Richmond Agitation/Sedation Scale (RASS)

The scale has been planned by a multidisciplinary team belonging to the Richmond University in Virginia. It's a score with 10 points. It can be done quickly. There are three steps relating to sedation - agitation level. The RASS has a good reliability. It is good if we compare it to other sedation scales. According to many studies the RASS is the first validated scale for its capability to get sedation even minimum changes for patients in ICU(12).

Observers' Assessment of Alertness/Sedation Scale (OAASS)

It is one of the most used scale in clinical practice.

- ready answer to the verbal call with normal tone (pt 5)
- delayed answer to the verbal call with normal tone (pt 4);
- answer only after repeated calls to high voice (pt 3);
- answer after little goad (pt 2)
- no answer after little goad (pt1)
- no answer to pain (pt 0)

Many other scale have been described (8):

Sedation Scoring System of Nisbet and Norris, New Sheffield Sedation Scale, Harris Scale, Comfort Scale, Motor Activity Assessment Scale, Bion Scale, Vancouver Sedative Recovery Scale, Brussels Sedation Scale, Addenbrooke's Hospital Scale, Sedation Score of Mackenzie and Grant, Sedation Score of Skeie et al, Sedation Score of Sury and Cole, Bloomsbury Sedation Score, Sedation Score of Cohen and Kelly, Linear Sedation Scale, Sedation Score of McMenemin et al, Sedation Score of Yate et al, Newcastle Sedation Scale, etc.

Objective Methods:

The technological progress allowed the development of objective methods to monitor sedation in ICU.

The same systems have been used in monitoring the surgical anaesthesia's depth.

Even though many clinical trials validated these monitoring systems, there are few studies focused on patients in ICU. So their adoption in ICU is still under definition (5).

However, they can be used with good reliability in sedated patients for whom applying the scoring system is not possible.

In the last few years many monitoring systems appeared. Unfortunately, none of them seems to be so good in daily practice for sedation monitoring in ICU because of their low sensibility, or simply for practical reasons (2)

Although they aren't supported by unquestionable clinical evidences, three monitoring instruments, still compared in many clinical studies, arouse intensivists' interest: Bispectral Index (BIS), AEP (Auditory Evoked Potentials) monitor, Cerebral State Monitor and Entropia.

Bispectral Index:

Bispectral index is a scale derived from the electroencefalografic analysis. It's based on a numerical value between 0 (deep anesthesia) and 100 (awake).

It is based on an empirical measurement, statistically derived, based on a very big EEG database. A BIS value between 50 and 60 is connected with a lower capability to answer to a verbal demand.

The loss of consciousness is about on 70. BIS values under 45 are connected with deep sedation and low consciousness.

This modern neurophysiological monitoring achieved big interest for its application during drugs sedation in ICU's patients.

Many clinical studies compared this monitoring instrument with clinical score (Ramsay, SAS...) (7, 13), but according to many authors, BIS is not reliable for clinical practice for the big interindividual variability observed with the same sedation level.

It could be used only compared with scoring systems, representing a subjective monitoring way.

AEP Monitor:

Evoked potentials (EP) are nervous system's elettrophysiological answers, strictly connected with a sensorial goad. We know three classes of EP based on their latency so we have Long Latency EP (100 millisecc) middle latency EP (10 millisecc) and short latency EP(millisecc). Long latency EP are suppressed under surgical anaesthesia. They are not useful for sedation monitoring. Middle latency EP appear during anaesthesia correlated with anaesthesia's level. Short latency EP can be recordered under sedation (5)

Auditory Evoked Potentials (AEP) are an electrical manifestation of brain response to an auditory goad. They are the simplest to be produced through suitable headphones. The EP in answer are recordered by

electrodes placed on the scalp. As we can use AEP for monitoring awareness or anaesthesia depth, so we can use AEP for monitoring sedation level in ICU's patients, even if we need other studies for their application (14)

Cerebral State Monitor (CSM):

It has been adopted to quantify, from 0 to 100, the effect of sedatives and anaesthetic drugs on the brain. Until now, it has been used to monitor anaesthesia's depth.

According to the authors there are not clinical trials about its use in ICU

However, a new comparative study (15) has been done with Bispectral Index during target-controlled propofol infusion (from minimum values, 0.5 mcg/ml, increasing the target).

It has shown a good correlation with BIS and the Observer's Assessment of Alertness/Sedation Scale with propofol increasing doses. But further studies shall validate its usefulness in ICU in sedation monitoring.

Entropy:

It's based on EEG. The awake patient's EEG is highly "untidy". The beginning of the sedation causes a more regular layout, a reduced entropy state.

The Entropy Monitor records a slow "state entropy" (EEG signal beyond 32 Hz) and a faster "response entropy" (frequencies raised beyond 47 Hz, produced by the frontal muscle).

It seems to provide a better changing sedation level prediction than BIS when used to monitor consciousness level in voluntary healthy patients while propofol and remifentanyl (17) were given. No clinical trials in scientific literature allow its use in ICU for sedation monitoring.

Analgesia Monitoring:

All patients in ICU feel pain; when they are deep sedated, with no resolution, they cannot communicate with the physicians and the nurses. Everybody knows pain damage: haemodynamic changes, psychological effects, damage of the immune system, catecholamine answer to the stress.

Pain must be treated. Ramsay wrote "it is inhumane not to adequately treat pain". Furthermore a good analgesia reduces sedatives doses necessary to keep a good sedation quality (1)

Main targets of pain management are:

- monitoring pain and at the same time patient's answer to analgesic treatment, using appropriate scoring systems
- record behavioural and physiological changes connected to the pain in unconsciousness patients and their changes in response to analgesic therapy (18)

In many ICU, pain is not systematically recorded; it has been shown that pain monitoring improves the quality of patients treatment (19). So physicians and nurses have to learn and use all pain scoring system.

Pain monitoring in consciousness patients:

The best indicator is patients' speech. Often in ICU the patient cannot verbally communicate because of endotracheal tube or tracheostomy.

In this case for pain monitoring must be used (18):

1) the Visual Analogue (VAS) Scale.

It is considered "the gold standard" for patients pain monitoring.

It is a horizontal line (10 cm) between two extremes corresponding to "no pain" and "the biggest imaginable pain". It is often used in ICU even if it has never been specifically tested.

2) the Numeric Rating (NRS) Scale, a 10 numbers (0-10) scale: 0 no pain, 10 the biggest imaginable pain". It seems to be the more used method, the preferred one by the nurses in ICU.

Pain monitoring in unconscious patients

In these cases, evaluating physiological parameters (HR, RR, BP), behavioural, neurovegetative phenomena (18) is necessary.

However, the reliability of these signs has been often discussed.

These clinical signs can't be referred just to pain. Besides there are too many conditions in which it is possible to discover an increase of heart rate, breath rate, blood pressure, especially in ICU!

So behavioural scale must be used, like the Behavioural Pain ones (with a score from 3 to 12). This score is easy to use and allows to adjust drugs in agreement with score changes. It is possible to value therapy impact on patient comfort (4).

Do not forget opioids damages given by prolonged overdosing in ICU. Their bad use can cause increase of weaning, haemodynamic instability, changes of the hepatic enzymogram, causing tolerance, abstinence sign, aroused by sudden interruption of the therapy (20).

In the last few years, remifentanyl produced a turn in the treatment of the pain in ICU.

Its quick metabolism by blood pseudocholinesterases allows remifentanyl to become a choice opioid for critical patients (21).

Conclusions:

The instrumental and clinical analgesia management is a hard challenge for the intensivist.

Nowadays recommendations lead intensivists to a correct use of sedation scales as subjective monitoring systems useful in sedation monitoring in ICU. In addition intensivists are recommended to pay constant attention to the technological innovations and to their further clinical evidences that will validate them.

- 1) Ramsay MA: "Sedation: from the past to the future". 13th World Congress of Anaesthesiologists, Paris 2004, L14.
- 2) Mondello E, Siliotti R, Gravino E, et al: "Sedation monitoring in ICU". *Minerva Anestesiol* 2005, vol.71, n.9, pgg.487-96.
- 3) Hole A: "Monitoring sedation in the ICU patient". *Clin Intensive Care* 1993, Suppl 2:27-29.
- 4) Fraser GL, Riker RR: "Monitoring sedation, agitation, analgesia, and delirium in critically ill adult patients". *Crit Care Clin* 2001 Oct;17(4):967-87.
- 5) Carrasco G: "Instruments for monitoring intensive care unit sedation". *Crit Care* 2000;4(4):217-225.
- 6) Costa J, Cabrè L, Molina R, Carrasco G: "Cost of ICU sedation: comparison of empirical and controlled sedation methods". *Clin Intensive Care* 1994;5:17-21.
- 7) Mondello E, Siliotti R, Noto G, et al: "Bispectral index in ICU: correlation with Ramsay Score on assessment of sedation level". *J Clin Monit Comput* 2002 Jul;17(5):271-7.
- 8) <http://www.shefa-online.net/khdm/ANESTH.html>
- 9) De Jonghe B, Cook D, Appere-De Vecchi C, Guyatt G, Meade M, Outin H: "Using and understanding sedation scoring systems: a systematic review". *Intensive Care Med* (2000). 26:275-285.
- 10) Ramsay MA, Savege TM, Simpson BR, Goodwin R: "Controlled sedation with alphaxolone-alphadolone". *BMJ* 1974;2:656-9.
- 11) Riker RR, Picard JT, Fraser GL: "Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients". *Crit Care Med* 1999;27:1325-9.
- 12) Ely WE, Truman B, Shintani A, et al: "Monitoring Sedation Status Over Time in ICU Patients – Reliability and Validity of the Richmond Agitation/Sedation Scale (RASS)". *IAMA*, June 11, 2003 – Vol 289, n.22, 2983-2991.
- 13) Simmons LE, Riker RR, Prato BS, Fraser GL: "Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation/Agitation Scale". *Crit Care Med* 1999 Aug;27(8):1499-504.
- 14) Schulte-Tamburen AM, Scheier J, Briegel J, Schwender D, Peter K: "Comparison of five sedation

scoring systems by means of auditory evoked potentials". *Intensive care Med* 1999;25:377-82.

- 15) Zhong T, Guo QL, Pang YD, Peng LF, Li CL: "Comparative evaluation of the cerebral state index and the bispectral index during target-controlled infusion of propofol". *Br J Anaesth* 2005 Dec;95(6):798-802.
- 16) Young CC: "Assessment of depth sedation". 13th World Congress of Anaesthesiologists, Paris 2004, C111c.
- 17) Bruhn J, Bouillon TW, Radulescu L et al : « Correlation of approximate entropy, bispectral index, and spectral edge frequency 95 (SEF95) with clinical signs of "anesthetic depth" during coadministration of propofol and remifentanyl ». *Anesthesiology* 2003;98:621-627.
- 18) Gravino E, Mondello E, Mediati R, et al: "Razionale delle linee guida SIAARTI per l'analgo-sedazione in Terapia Intensiva". *Minerva Anestesiol* 2005;71(Suppl.1 al n.10):87-9.
- 19) Lewis KS, Whipple JK, Michael KA, Quebbeman EJ: "Effect of analgesic treatment on the physiological consequences of acute pain". *American Journal of Hospital Pharmacists* 1994;51: 1539-1554.
- 20) Coluzzi F, Mattia C, Ambrosio F, et al: "Guidelines in analgesia: tolerance and dependence". *Minerva Anestesiol* 2005;71(Suppl.1 al n.10):96-8.
- 21) Muellejans B, Lopez A, Cross MH, et al: "Remifentanyl versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial". *Critical Care* 2004, 8:R1-R11.

ANALGO-SEDATION OF MAJOR BURN PATIENTS OUTSIDE THE OPERATING ROOM

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Introduction:

Burn injury is among the most severe forms of trauma. When considering a major burn (MB) patient, we must keep in mind that we are approaching a patient with:

- a systemic inflammatory response (1,2)
- a systemic heat-shock response (HSR) (3)

- one of the most severe form of trauma
- a various forms of psychological distress (e.g., posttraumatic stress disorder, major depression or delirium)
- one of the most severe forms of extremely variable acute pain (4-6) with need for analgo-sedation outside of the operatory room

The pain experienced by these patients is a constant background pain of relatively low intensity on which are superimposed short-lasting peaks of severe to excruciating pain associated with the numerous therapeutic procedures performed on a daily basis during their hospital stay (4-6). In addition burn pain is extremely variable from one patient to another and procedure-related pain requires frequent assessment and individual titration for effective pain management because wide fluctuations over time (even in the same procedure) (7). Because of this wide variability in the pain experienced, pain management needs to be highly tailored during high pain procedure,

Among the therapeutic procedures major burns undergo, the most common not surgical procedure performed outside the operatory room involves the daily change of dressings performed in patient 's room or in special bath-room (8). This procedures as a unique feature. During patient bathing or simple change of dressing patients can be turned over, sat up, or positioned almost prone while needing deep analgesia and/or sedation. The first change of dressing after skin grafting is probably the most painful procedure. It also a source of great anxiety because of the immediate and first confrontation with the result of skin grafting in not sedated patients

Multimodal approach to pain relief during major burn dressing:

Nociceptive signals initiated by a tissue injury are transmitted by polymodal C-fiber and A-fiber nociceptors to spinal cord dorsal horn neurons (9). This injury-induced intense afferent barrage activates a range of neurotransmitters and substances, including the excitatory aminoacids (EAA) aspartate and glutamate, substance P and CGRP, resulting in exaggerated responses of dorsal horn neurons and facilitation of further input to the dorsal horn (central sensitization or pain memory) (10,11).

A variety of basic science studies indicate that this facilitation process leads to enhanced pain sensitivity (hyperalgesia), pain to light tactile stimuli (allodynia) and prolonged, persistent pain after tissue injuries (9)

Recent preclinical and clinical studies give strong evidence that neuronal hypersensitivity and nociception after surgical incision is mainly maintained by the afferent barrage of sensitized nociceptors across the perioperative period. This is in contrast to pain states of

other origin in which prolonged hypersensitivity is initiated during the injury. Therefore, not timing but duration and efficacy of an analgesic and antihyperalgesic intervention are most important for treating pain and hyperalgesia after surgery (12-14).

Several therapeutic approaches have been studied to provide analgesia, comfort, or sedation during these procedures (15) using opiates alone or in combination with acetaminophen, or non-steroidal anti-inflammatory drugs (NSAID), benzodiazepine, propofol or ketamine (16-20)

Opiates:

Opiates remain the most common form of analgesic therapy in the pain management of patients with burns (17). However because of increased opiate requirements, optimal relief of burn pain continues to be a problem for these patients. Conventionally, large doses of potent opioids are delivered either by repeated IM or IV injections to alleviate procedure-related pain. Very often the analgesia provided by these regimens is inadequate with adverse side effects (16).

In order to tailor opioids delivering patient controlled analgesia (PCA) has been proposed in burn patients to self administer small predetermined doses of analgesic medication within limits prescribed by their physician. PCA with a potent, rapid onset and a relatively short-acting opioid offers a method of providing pain relief during burn dressing changes. resulting in improved pain relief, avoidance of over- and under-medication, and greater patient satisfaction (16,17). Prakash et al found that the optimal PCA-fentanyl demand dose in our study was 30 mcg after an IV initial loading dose of 1 mcg/kg and a lockout interval of 5 minutes (16).

Even though with PCA, the burn patient can titrate his or her medication according to need, most of burn patients have burns in both upper limbs thus abolishing the use of PCA

Non-steroidal anti-inflammatory drugs (NSAID) and Acetaminophen:

Nonopioid analgesics are often used for the treatment of acute, postoperative pain (19)

A recent study by Ong (21) analysing RCTs on preemptive analgesia for postoperative pain showed that systemic NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores.

Systematic review of randomized trials have confirmed the analgesic efficacy of acetaminophen, a classic NSAIDs, and selective COX-2 inhibitors after minor surgery (22-23). They act on peripheral and central sites

and interfere with pain mechanisms that are different from the opioid system.

A recent meta-analysis of RCT showed that there is evidence that the combination of non-steroidal anti-inflammatory drugs with patient-controlled analgesia morphine offers some advantages over morphine alone (24). The combination of several non-opioid analgesics may produce an additive or even synergistic effect. They conclude that optimal multimodal postoperative analgesia regimens should be identified in randomized and well-designed, large studies (24).

Patients who receive non-opioid analgesics in conjunction with morphine PCA are expected to consume less morphine to achieve satisfactory pain relief as compared with those who receive morphine alone that are attributable to the non-opioid analgesic (24)

Although NSAIDs increase the risk of surgical bleeding, the incidence of this complication is low. In particular settings, however, that risk may outweigh the benefit (14). Prolonged use of NSAIDs may produce renal failure (25).

Ketamine:

Ketamine is an excellent analgesic producing at whole dosage the so called "dissociative anesthesia" (e.g., analgesia, separation of personality and environment, maintenance of consciousness) (26). Ketamine provides anesthesia without a need for mask. It means the patient can be turned over, sat up, bathed, or positioned in any way with a minimum of hazard (3). It has a rapid onset (intravenous concentrations reach peak level within 1 minute) and a short duration (15–30 minutes) of action. Moreover, recovery is rapid as well. In addition, ketamine dosing has a wide safety margin compared with benzodiazepine and narcotic agents (27,28)

Ketamine also stimulates the cardiovascular system primarily by direct central sympathetic stimulation. Circulatory catecholamine levels also are increased by inhibition of reuptake.

The advantages of this vasoconstrictor action, contrary to the vasodilatation caused by virtually all other anaesthetic agents, are in MB all of the following:

- better manage of the blood pressure during a given rapid and continuous blood loss
- reduced surface blood loss
- heat loss from the skin
- muscle tone and protective airway reflexes

Ketamine also stimulates HSR increasing the survival rates of experimental cutaneous, free myocutaneous, and

osteomyocutaneous flaps previously subjected to heat shock (29). It has also been shown to reduce the production of TNF, IL-6 and reactive oxygen metabolites in human blood cells and to have antithrombogenic property (30-31).

Despite all these evident advantages, widespread acceptance of ketamine as a sole drug for usage in burn has shown a slow increase because its psychological side-effects although administration of a benzodiazepine (19). When racemic ketamine is used in large doses as a single agent, or administered rapidly (<1 minute) floating sensations, vivid dreams, hallucinations, and delirium are still high (32).

In addition the operator as during administration of other anaesthetic drugs (i.e. propofol) loose during the change of dressing the capacity to evaluate the real patient's pain.

When Ketamine is studied at subanesthetic doses, its analgesic efficacy correlates well with its inhibiting action on NMDA receptor-mediated pain facilitation (33) and a decrease in activity of brain structures that respond to noxious stimuli (34).

NMDA receptors participate in the development and maintenance of what can be called "pathologic pain" after tissue injury: increased pain perception as a result of pain sensitization, in part from synaptic plasticity (35,36).

Being a non competitive N-methyl-d-aspartate (NMDA) receptor antagonist, ketamine reduces the excitatory effect of glutamate. Although the NMDA blockade is believed to mainly determine the analgesic properties of ketamine, the drug also interacts with opioidergic, mu as well as cholinergic, noradrenergic, dopaminergic, and serotonergic receptors (37). Ketamine binds noncompetitively to the phencyclidine binding site of NMDA receptors but also modifies them via allosteric mechanisms (38,39).

Although the mechanisms that allows ketamine to be an analgesic and opiate-sparing agent after opiate exposure remain poorly understood, two emerging concepts may be important. First, at neuronal synapses, scaffolding proteins such as postsynaptic density protein-95 (PSD-95) and postsynaptic density protein-93 (PSD-93) connect NMDA receptors to the cytoskeleton and to key signaling systems, such as neuronal nitric oxide synthase (35,40-41). Second, in sensitization or developing tolerance, activated protein kinase C and tyrosine kinase cascades facilitate association of key signaling molecules with PSD proteins and NMDA receptors (35,42). This activates protein kinases, resulting in NMDA receptor phosphorylation and up-regulation. Thus, a ketamine-induced decrease in unfavourable PSD interaction with protein kinases and pain signaling systems may represent a common mechanism

underlying reduced pain sensitization and opiate tolerance phenomena (39). Ketamine therefore represents a promising modality in several perioperative strategies to prevent pathologic pain (39).

Ketamine has been shown to reduce morphine requirements and PONV in the first 24 h after surgery (20).

NMDA receptors should be blocked during ongoing intraoperative as well as postoperative transmission of nociceptive impulses. Postoperative mobilization may elicit delayed waves of afferent painful stimuli. Regarding acute opiate tolerance-related phenomena, it is as yet unclear whether ketamine is best administered before first use of opioids (39). For prevention of pathologic pain after severe tissue injury, ketamine administration should cover the entire duration of high-intensity noxious and inflammatory stimulation, not simply the initial trauma (3).

Alpha 2 agonist:

Clonidine has also shown to reduce pain without causing pruritus or respiratory depression (8,22). Clonidine when used in healthy volunteers has been shown negligible cardiorespiratory side effects up to 4 mcg/kg/min EV (43). Continuous clonidine infusion has been shown to be useful to control postoperative pain showing a sparing-morphine effect (44). Animal studies have demonstrated that mu-opioid receptors that coexist with alpha-2- adrenoceptors in the spinal cord may act in synergy after activation by alpha-2-adrenoceptor agonists (45).

Clonidine is also effective to attenuate the perioperative stress response (46-49)

Clonidine has also a positive effect on the kidneys increasing diuresis and natriuresis (50).

The use of opioid antagonists combined with alpha-2 adrenergic agonists is also a feasible approach to the management of opioid withdrawal (51) also in the perioperative period.

No pharmacologically significant adverse effects have been discovered for alpha-2-adreno-ceptor agonists, other than an extension of their known physiological effects: hypotension and bradycardia. However, bradycardic arrhythmias as well as hypovolaemia are contraindications for the use of clonidine. Bolus dosing has to be carefully administered as cardiovascular side effects such as temporary hypertension, hypotension and bradycardia may occur (52).

Because clonidine withdrawal may precipitate hypertensive crises, patients should be weaned off clonidine gradually.

Propofol:

Propofol is a well know anesthetic drug without analgesic property. PCA with propofol can be used in burn patients undergoing nonoperative procedures. To provide an effective sedation state, authors suggest to initially titrate the bolus to achieve a significant decrease of BIS or a clinically effective state of sedation and to abolish the lockout interval (8).

Other drugs:

Antidepressants appear to enhance opiate-induced analgesia while anticonvulsants are useful in the treatment of sympathetically maintained pain following burns (19). Alternative methods of pain treatment using acupuncture, hypnosis or stress reducing therapy have also been used with a various degrees of success (52-55). Other forms such as transcutaneous electrical nerve stimulation (TENS), psychological techniques, topical and systemic local anaesthetics are also useful adjuncts (19,55)

Conclusions:

A multimodal approach to perform adequate analgesia and sedation in conscious major burn patients is needed. Because most of the patients have burn of the upper limb the role of PCA is restricted to selected patients. However whenever possible analgesia must be tailored taking into account patient's pain score. As a consequence sedation should be administered according to a sedation degree that allows patient pain evaluation

References:

1. Cone JB, Wallace BH, Lubansky HJ, Caldwell FT. Manipulation of the inflammatory response to burn injury. *J Trauma* 1997;43:41-6.
2. Hansbrough JF, Wikstrom T, Braide M, et al. Neutrophil activation and tissue neutrophil sequestration in a rat model of thermal injury. *J Surg Res* 1996; 61:17-22.
3. Ceber M, Salihoglu Ketamine May Be the First Choice for Anesthesia in Burn Patients *Journal of Burn Care & Research* 2006; 27:760-62.
4. Ashburn MA. Burn pain: the management of procedure-related pain. *J Burn Care Rehabil* 1995;16:365-71.
5. Latarjet J, Choinie`re M. Pain in burn patients. *Burns* 1995;21: 344-8.
6. Kowalske K, Tanelian D. Burn pain: evaluation and management. *Anesthesiol Clin North America* 1997;15:269-83.
7. MacLennan N, Heimbach DM, Cullen BF. Anesthesia for major thermal injury. *Anesthesiology* 1998; 89:749-70.

8. Coimbra C, Manon Choiniere M, Hemmerling TM Patient-Controlled Sedation Using Propofol for Dressing Changes in Burn Patients: A Dose-Finding Study *Anesth Analg* 2003;97:839–42.
9. Treede R-D, Handwerker HO, Baumgartner U, et al. Hyperalgesia and allodynia: taxonomy, assessment, and mechanisms. In: Brund K, Hermann OH, editors. *Hyperalgesia: molecular mechanisms and clinical implications*. Seattle: IASP Press; 2004. pp. 3–15.
10. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; 13:203–210.
11. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science* 2000; 288:1765–1768.
12. Wall PD. The prevention of postoperative pain. *Pain* 1988; 33:289–290.
13. Pogatzki-Zahn EM, Zahn PK From preemptive to preventive analgesia *Curr Opin Anaesthesiol* 19: 551–555.
14. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002; 96:725–741.
15. Ashburn MA. Burn pain: the management of procedure-related pain. *J Burn Care Rehabil* 1995;16:365–71.
16. Prakash S, Fatima T, Mridula Pawar M patient-controlled analgesia with fentanyl for burn dressing changes *Anesth Analg* 2004;99:552–5.
17. Sim KM, Hwang NC, Chan YW, Seah CS. Use of patient controlled analgesia with alfentanil for burns dressing procedures: a preliminary report of five patients. *Burns* 1996;22:238–41.
18. Finn J, Wright J, Fong J, Mackenzie E, Wood F, Leslie G, Gelavis A. A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. *Burns*. 2004 3:262-8.
19. Pal SK, Cortiella J, Herndon D Adjunctive methods of pain control in burns *Burns*. 1997 Aug;23(5):404-12.
20. Peri-operative ketamine for acute post-operative pain: Quantitative and qualitative systematic review (Cochrane review) *Acta Anaesthesiol Scand* 2005; 49: 1405—1428.
21. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* 2005; 100:757–773.
22. Rømsing J, Møiniche S: A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for post-operative pain. *Acta Anaesthesiol Scand* 2004; 48:525–46.
23. Straube S, Derry S, McQuay HJ, Moore RA: Effect of preoperative COX-IIselective NSAIDs (coxibs) on postoperative outcomes: A systematic review of randomized studies. *Acta Anaesthesiol Scand* 2005; 49:601–13.
24. Elia N, Lysakowski C, Trame MR Does Multimodal Analgesia with Acetaminophen, Nonsteroidal Antiinflammatory Drugs, or Selective Cyclooxygenase-2 Inhibitors and Patient-controlled Analgesia Morphine Offer Advantages over Morphine Alone? Meta-analyses of Randomized Trials *Anesthesiology* 2005; 103:1296–1304.
25. Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F, Ebrahim S, Escobar G, Jage J, Pocock S, Velo G, Langman MJ, Bianchi PG, Samama MM, Heitlinger E: Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. *Br J Anaesth* 2002; 88:227–33.
26. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* 1966;45:29–40.
27. Green SM, Clark R, Hostetler MA, Cohen M, Carlson D, Rothrock SG. Inadvertent ketamine overdose in children: clinical manifestations and outcome. *Ann Emerg Med* 1999; 34:492–7.
28. Green SM, Li J. Ketamine in adults: what emergency physicians need to know about patient selection and emergence reactions. *Acad Emerg Med* 2000;7:278–81.
29. Nader Meyer T, Lazaro Da Silva A. Ketamine reduces mortality of severely burnt rats, when compared to midazolam plus fentanyl. *Burns* 2004;30:425–30.
30. Larsen B, Hoff G, Wilhelm W, Buchinger H, Wanner GA, Bauer M. Effect of intravenous anesthetics on spontaneous and endotoxin-stimulated cytokine response in cultured human whole blood. *Anesthesiology* 1998; 89:1218–27.
31. Atkinson PM, Taylor DL, Chetty N. Inhibition of platelet aggregation by ketamine hydrochloride. *Thromb Res* 1985; 40:227.
32. Green SM, Sherwin TS. Incidence and severity of recovery agitation after ketamine sedation in young adults. *Am J Emerg Med* 2005; 23:142–4.
33. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM: Effect of racemic mixture and the (S)-isomer of ketamine on temporal and spatial summation of pain. *Br J Anaesth* 1996; 77:625–31.

34. Langso JW, Kaisti KK, Aalto S, Hinkka S et al Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 2003; 99:614–23.
35. Petrenko AB, Yamakura T, Baba H, Shimoji K: The role of N-methyl-D-aspartate receptors in pain: A review. *Anesth Analg* 2003; 97:1108–16.
36. Cairns BE, Svenson P, Wang K, Hupfeld S, Graven-Nielsen T, Sessler D, Berde CB, Arendt-Nielsen L Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. *J Neurophysiol* 2003; 90:2098–105.
37. Sprenger T, Valet M, Woltmann R, Zimmer C, Freynhagen R, Kochs FE, Tolle TR, MD, Wagner KJ, Imaging Pain Modulation by Subanesthetic S-(+)-Ketamine *Anesth Analg* 2006;103:729–37.
38. Orser BA, Pennefather PS, MacDonald JF: Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. *Anesthesiology* 1997; 86:903–17.
39. Himmelsehe S, Durieux ME Ketamine for Perioperative Pain Management *Anesthesiology* 2005; 102:211–20.
40. Tao YX, Rumbaugh G, Wang GD, Petralia RS, Zhao C, Kauer FW, Zhuo M, et al. Impaired NMDA receptor mediated postsynaptic function and blunted NMDA receptor-dependent persistent pain in mice lacking postsynaptic density protein-93. *J Neurosci* 2003; 23:6703–12.
41. Liaw WJ, Zhang B, Tao F, Yaster M, Johns RA, Tao YX: Knockdown of spinal cord postsynaptic density protein-95 prevents the development of morphine tolerance in rats. *Neuroscience* 2004; 123:11–5.
42. De Leon-Casasola OA: Cellular mechanisms of opioid tolerance and the clinical approach to the opioid tolerant patient in the postoperative period. *Best Pract Res Clin Anaesthesiol* 2002; 16:521–5.
43. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. *Br J Anaesth.* 2001; 86:5-11 *British Journal of Anesthesia* 2001; 86:5-117.
44. Baker AK, Hoffmann VL, Meert TF. Interactions of NMDA antagonists and an alpha 2 agonist with mu, delta and kappa opioids in an acute nociception assay. *Acta Anaesthesiol Belg* 2002;53:203–12.
45. Ossipov MH, Suarez LJ, Spaulding TC. Antinociceptive interactions between alpha 2-adrenergic and opiate agonists at the spinal level in rodents. *Anesth Analg* 1989;68:194–200.
46. Anand RS, Ochroch AE, Neligan PJ Alpha -2-Adrenoceptor Agonist Therapy in Perioperative Medicine and Critical Care *Contemporary Critical Care* 2005; 2:1-10.
47. Wijeyesundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 2003;114:742–752.
48. Wallace AW, Galindez D, Salahieh A, et al. Effect of clonidine on cardio-vascular morbidity and mortality after noncardiac surgery. *Anesthesiology* 2004; 101:284–293.
49. Wijeyesundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 2003;114:742–752.
50. Kulka PJ, Tryba M, Zenz M. Preoperative alpha2-adrenergic receptor agonists prevent the deterioration of renal function after cardiac surgery: results of a randomized, controlled trial. *Crit Care Med* 1996; 24:947–952.
51. Gowing L, Ali R, White J Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database Syst Rev.* 2006 Jan 25;(1).
52. Tonner PH, Scholz J. Clinical perspectives of alpha2-adrenoceptor agonists. *Current Opinion in Anaesthesiology* 1996; 9:471–480.
53. Lewis SM, Clelland JA, Knowles CJ, et al. Effects of auricular acupuncture-like transcutaneous electric nerve stimulation on pain levels following wound care in patients with burns: a pilot study. *J Burn Care Rehabil* 1990;11:322–9.
54. Frenay MC, Faymonville ME, Devlieger S, et al. Psychological approaches during dressing changes of burned patients: a prospective randomised study comparing hypnosis against stress reducing strategy. *Burns* 2001;27:793–9.
55. Meyer WJ, Marvin JA, Patterson DR, et al. Management of pain and other discomforts in burned patients. In: Herdon DN, ed. *Total burn care*. 2nd ed. WB Saunders, 2002;747–65.

THE USE OF TCI SIMULATORS FOR RESIDENT TEACHING

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In the United States, the Federal Drug Administration has not approved any TCI devices for clinical use. The absence of these devices is likely a major determinant in the lower prevalence of Total Intravenous Anesthesia techniques in the United States as compared to Europe. However, as there is growing evidence for the utility of total intravenous anesthesia, it is imperative that anesthesia trainees develop adequate experience in total intravenous anesthesia. Because we do not have infusion systems to predict the pharmacokinetic variables and implement the appropriate concentration changes, we have no option but to use TCI simulators to provide our trainees with the necessary knowledge of pharmacokinetic and pharmacodynamic considerations for each drug, as well as understanding the influence of the patient covariates that contribute to inter-individual variability. A key portion of this is understanding the influence of plasma-effect site equilibration delays on the time course of drug effect. Many TCI systems have simulation settings that can be used for teaching purposes. For example, Stanpump (Palo Alto, CA) is a DOS-based program that can be run during an anesthetic from a laptop computer. I typically provide a resident with literature describing predicted drug concentrations for a specific drug the night before an anesthetic. I instruct the resident to input the patient characteristics and perform simulations to evaluate the proposed drug dosing. We also look at responses to overdose and underdose. Many residents are surprised by the relatively phlegmatic response to increases and decreases in infusion rate, and appreciate the need for a bolus dose to quickly increase concentration, and a (temporary!) stop in infusion if one needs to quickly decrease drug concentration. Propofol is the drug we usually simulate. Desired endpoints are an appreciation for expected onset and offset times with steady state infusion and the consequences of a bolus dose. Residents also learn about the potential accumulation of propofol over time with steady state infusions, and the severe consequences of giving infusions over many hours that are not adequately titrated to drug effect. Once we decide on appropriate infusion rates, we use STANPUMP in "real time" during the anesthetic. Specifically, we input patient characteristics before starting, so STANPUMP can tailor the anesthetic to the individual patient. During the anesthetic we enter infusion rates into STANPUMP concurrently with adjusting the pump. Residents learn to consider the predicted concentration as part of the calculus of precise anesthetic titration. Differences between predicted and actual patient response provide an appreciation of intra-individual variability. Additionally, the resident can compare the disequilibrium between the plasma and effect site predicted by STANPUMP with the real time hysteresis observed using a BIS monitor. The above techniques of course apply not only to propofol, but many opioids and sedatives that are administered as an

infusion. Simulation of dexmedetomidate plasma and effect site concentrations during ICU sedation is also a useful exercise. TCI simulation is a useful teaching technique in the United States. Indeed, simulation is our only option until TCI devices become available to US practitioners.

TEACHING BASIC IV PHARMACOLOGY: WHAT CONCEPTS DO YOU NEED TO TEACH?

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Some knowledge of basic pharmacology is beneficial in terms of understanding and predicting physiologic responses to IV drugs; their variability and expected time-course. Important concepts may be linked to how the drug is distributed, metabolized or eliminated in the body, i.e. pharmacokinetics; and to how the drug produces a clinical action; i.e. pharmacodynamics. Visualization in simple figures and no use of advanced mathematics are key-stones in teaching these basic items. Important aspects of pharmacokinetics will be how the level and variations in plasma concentration may be determined and predicted from knowing the patient characteristics (especially weight, but also age and height), dosing schedule, the application of a 3 compartment model and speed of elimination of active drug, either by metabolism or direct renal excretion. Important concepts are volume of distribution, clearance and 1.order elimination. It is also very important to know the context sensitive elimination concept; i.e. that the rate of plasma concentration decline of a drug given regularly will for most drugs correlate inversely with the duration of administration. If we know the basic pharmacokinetics of distribution and elimination, we will also be able to dose a drug by adjusted bolus doses and infusion aiming at keeping a constant level of drug in plasma, i.e. target control infusion. In understanding clinical effects of a drug, it is always useful if we know the basic mechanism(s) and site(s) of drug action. Knowing these items, or just by studying the course of plasma concentration and concomitant development of clinical effect, we may introduce the important concept of delay in action, the $T_{1/2 ke0}$, or time to maximum effect from a bolus dose. Different types of dose effect relationship curves are important: is there any lower threshold for start of effect and any upper threshold for maximal effect? Is the dose-response curve linear or curved? Interindividual differences in sensitivity to drugs are important, either caused by age, tolerance or genetic factors. Further; different aspects of additive effects (supra- or infra-additive) when drugs are given together, and also the level of dosing needed for wanted

effects versus occurrence of side-effects. The receptor concept is very important for anaesthetic drugs, including the antagonist-agonist concept.

Pragmatic (but still fairly correct) definitions:
 Distribution volume: The volume needed for distribution if all drug in the body should have the same concentration as in the plasma.

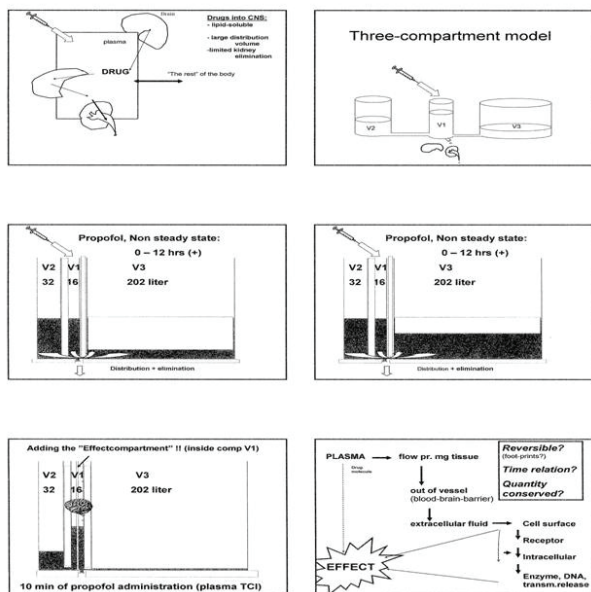
Clearance: The recalculated amount of plasma which is fully cleared of all drug during a time period. (recalculation from the actual amount plasma cleared by something between 0-100%)

First order elimination: a fixed proportion of drug is cleared from the plasma at any time (in contrast to zero-order elimination when a fixed amount of drug is eliminated at any time)

$T_{1/2 ke0}$: The time taken to have 50% of the concentration in plasma equilibrated into the effect site (effect site starting at 0) if the plasma level can be kept constant

Other topics to be covered will depend on the experience and interests of delegates. These may include:

1. Practical aspects of TIVA and TCI
2. Principles of pharmacokinetics
3. Principles of target-controlled infusion (TCI)
4. Brief history of the development of the TCI concept
5. Brief history of the development of TCI systems
6. TCI opioids
7. Pharmacokinetic interactions
8. Pharmacodynamic interactions
9. Accuracy of TCI systems
10. Effect-site targeted TCI
11. Comparisons of available models for commonly used drugs
12. Depth of anaesthesia monitoring
13. Incidence of awareness during TIVA



MONITORING NEUROMUSCULAR BLOCK: IS IT STILL USEFUL?

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Marked interindividual variability in response to the effects of muscles relaxants is well known and for many years, stimulation of the ulnar nerve using train-of-four (TOF) in association with monitoring of the adductor pollicis has been used to determine the time course and intensity of neuromuscular blockade. It has become the gold standard for monitoring of neuromuscular transmission. However, new modes and sites of stimulation have been introduced to assess the time course and intensity of neuromuscular blockade from onset until complete recovery of neuromuscular transmission.

HANDS ON TCI: PRACTICAL CASES

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The workshop will be run in an informal manner, to encourage interaction between delegates and the workshop leaders, and to allow delegates to develop "hands-on" familiarity with current infusion pumps. The workshop will be based on discussions of a series of clinical cases.

Onset of neuromuscular block:

After induction of anaesthesia, the intensity of neuromuscular blockade must be assessed to determine the optimum time for tracheal intubation. Although intubating conditions can be affected by the depth of anaesthesia, good intubating conditions might not be obtained unless complete blockade of the respiratory muscles is obtained. Bencini and Newton have suggested that good intubating conditions could be obtained before complete paralysis at the adductor pollicis (1). As previously discussed, paralysis of the adductor pollicis lags behind relaxation of the

respiratory and the laryngeal adductor muscles. These findings could explain the discrepancies observed between the intubating conditions and the degree of peripheral neuromuscular blockade. If a dose sufficient to block the diaphragm or the laryngeal muscles is given, neuromuscular blockade at the adductor pollicis is not usually achieved when full relaxation of the respiratory muscles occurs. At the opposite, following administration of a subparalysing dose of a NDMR at the respiratory muscles, their function may recover in the 3-6 minutes range, while adductor pollicis block becomes more intense (2). Therefore monitoring of an other peripheral muscle during induction of anaesthesia could give more accurate information to determine the optimal time for intubation.

Among the other peripheral muscles which can be easily monitored, the orbicularis oculi has been considered as an accurate monitoring of resistant muscles such as the diaphragm (2) or the laryngeal adductor muscles (3). Le Corre et al. has demonstrated that when a NDMR was given at a dose sufficient to block respiratory muscles, complete blockade at the orbicularis oculi following train-of-four stimulation might predict good intubating conditions (4). Following 0.5 mg/g atracurium, intubation could be provided in all the patients approximately 1 minute before complete paralysis at the adductor pollicis (3). However, the orbicularis oculi which is innervated by the temporal branch of the facial nerve is a thin muscle which covers the eyelid. In initial studies, movements recorded over the superciliary arch were attributed to the orbicularis oculi but close inspection of the response to facial nerve stimulation suggests that the movements observed over the superciliary arch corresponded to the contraction of the corrugator supercilii (5). The corrugator supercilii receives, like the orbicularis oculi, facial innervation and pulls the eyebrow towards the nose. It may be a better choice than the adductor pollicis or the orbicularis oculi because its onset of paralysis approaches that of the laryngeal adductor muscles (5). Since the sensitivity of the corrugator supercilii to NDMR is close to that of the laryngeal adductor muscles (Figure 1), its paralysis probably indicates complete blockade of almost all muscles whose relaxation is required for good intubating conditions. When a dose insufficient to block the respiratory muscles is given, monitoring of the adductor pollicis can be misleading because absence of a response at the adductor pollicis does not guarantee adequate intubating conditions.

Maintenance of neuromuscular paralysis:

The type of stimulation that one may elect to use intraoperatively will be influenced by the depth of block required for surgery. For practical reasons it is almost impossible to monitor the response of the diaphragm or the abdominal muscles during surgery. Disappearance of

train-of-four (TOF) at the adductor pollicis does not necessarily indicate paralysis of the vocal cords or the diaphragm and does not eliminate the possibility of hiccups or extrusion of abdominal contents. During that phase of so called "period of no response", because no response to TOF occurs, two different techniques may allow the evaluation of very intense blockade when complete paralysis of the diaphragm is sought. Complete absence of post-tetanic count (PTC) suggests near 100% receptor occupancy with ablation of diaphragm response. The number of responses in the PTC is related inversely to the depth of neuromuscular block. PTC can also be used to predict the time that will be required for return of spontaneous twitch (6). The major drawback of the technique is that it cannot be repeated more often than every 5 minutes as facilitation of subsequent responses may occur. Monitoring of the corrugator supercilii, using a TOF stimulus may also have a role during surgery because the response of the corrugator supercilii is a good reflection of the paralysis of the respiratory muscles (5).

When profound blockade is not required, monitoring at the adductor pollicis using TOF is sufficient and allows easier assessment of antagonism of relaxation at the end of the case. When a twitch depression of approximately 90% is sought, usually one twitch at the adductor pollicis is visible. In this situation, neither PTC nor TOF at the corrugator supercilii provides more relevant information.

Recovery and detection of residual paralysis: The recovery phase begins with the reappearance of the fourth response to the TOF. The major goal of neuromuscular monitoring during recovery is to detect residual paralysis which can occur in at least 10% of the patients (7) and sometimes in more than 40% of the patients in the recovery room when there is no use of a nerve stimulator and no reversal (8). It is recommended to monitor a muscle whose recovery will occur after recovery of respiratory muscles. Antagonism should never be attempted on the basis of information given by the TOF at the orbicularis oculi because its reappearance may be still associated with intense paralysis of muscles other than the diaphragm but which are also involved in respiration.

When the fourth response at the TOF at the adductor pollicis reappears, neuromuscular block is usually less than 75%. When the adductor pollicis has almost completely recovered, it can be assumed that no residual paralysis exists at both the diaphragm (9) and the laryngeal adductor muscles. However respiratory failure due to upper airway weakness (10), impairment of the muscles of the pharynx (11;12) or of the ventilatory response to hypoxia (13) exists even in the presence of nearly complete recovery of the adductor pollicis. Therefore monitoring needs to be used judiciously.

Visual or tactile assessment of fade when the TOF ratio is above 40% is very difficult even for experienced anaesthesiologists and cannot exclude significant residual paralysis (14). As the 50Hz tetanus is not more accurate than TOF in detecting fade, its usefulness in monitoring recovery is doubtful (14). Double-burst stimulation (DBS) can detect fade more easily than TOF, and improves manual assessment of neuromuscular block. However fade cannot be detected with DBS when the TOF ratio is above 60% (15) and does not eliminate the risk of remaining residual paralysis (16). In cooperative patients a few clinical tests may reveal evidence of muscular weakness. The head lift test or the ability to lift the head for 5 s is passed for TOF ratio ranging from 45 to 75%. Kopman et al. have recently demonstrated that the most sensitive clinical tests were the ability to retain a tongue depressor clenched between the teeth or the lack of visual disturbance (17). However all clinical tests are imprecise and of limited use at the end of a case. In daily clinical practice the detection of residual paralysis could be improved by the use of objective measurements. Mechanomyography or electromyography are more research tools, and acceleromyography is more convenient in clinical practice. The objective measurement of the TOF ratio is the best way to detect and avoid residual paralysis in the recovery room. A TOF ratio above 0.9 at the adductor pollicis confirms the absence of residual block even at the upper airway muscles (17).

Conclusion: The site and type of monitoring should be adapted to requirements during induction, maintenance and recovery from anaesthesia and neuromuscular block. A fast onset, resistant muscle, such as the corrugator supercilii, appears best suited for tracheal intubation and maintenance of deep neuromuscular block whereas the adductor pollicis is better adapted for monitoring of less intensive levels of paralysis and recovery. New methods of stimulation and recording of the evoked response have increased the sensitivity of neuromuscular monitoring during recovery from NMB.

References:

(1) Bencini AF, Newton DE. Rate of onset of good intubating conditions, respiratory depression and hand muscle paralysis after vecuronium. *Br J Anaesth* 1984; 56:959-965.

(2) Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. *Anesthesiology* 1990; 73:870-875.

(3) Debaene B, Beaussier M, Meistelman C, Donati F, Lienhart A. Monitoring the onset of neuromuscular block at the orbicularis oculi can predict good intubating conditions during atracurium-induced neuromuscular block. *Anesth Analg* 1995; 80:360-363.

(4) Le Corre F, Plaud B, Benhamou E, Debaene B. Visual estimation of onset time at the orbicularis oculi after five muscle relaxants: application to clinical monitoring of tracheal intubation. *Anesth Analg* 1999; 89:1305-1310.

(5) Plaud B, Debaene B, Donati F. The corrugator supercilii, not the orbicularis oculi, reflects rocuronium neuromuscular blockade at the laryngeal adductor muscles. *Anesthesiology* 2001; 95:96-101.

(6) Viby-Mogensen J, Howardy-Hensen P, Chraemmer-Jorgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense non depolarizing neuromuscular blockade. *Anesthesiology* 1981; 55:458-461.

(7) Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. *Anesthesiology* 1988; 69:272-276.

(8) Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; 84:394-395.

(9) D'Honneur G, Slavov V, Merle JC, Kirov K, Rimaniol JM, Sperry L et al. Comparison of the effects of mivacurium on the diaphragm and geniohyoid muscles. *Br J Anaesth* 1996; 77:716-719.

(10) D'Honneur G, Gall O, Gerard A, Rimaniol JM, Lambert Y, Duvaldestin P. Priming doses of atracurium and vecuronium depress swallowing in humans. *Anesthesiology* 1992; 77:1070-1073.

(11) Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology* 1997; 87:1035-1043.

(12) Sundman E, Witt H, Olsson R, Ekberg O, Kuylenstierna R, Eriksson LI. The incidence and mechanisms of pharyngeal and upper esophageal dysfunction in partially paralyzed humans: pharyngeal videoradiography and simultaneous manometry after atracurium. *Anesthesiology* 2000; 92:977-984.

(13) Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology* 1993; 78:693-699.

(14) Dupuis JY, Martin R, Tessonier JM, Tetrault JP. Clinical assessment of the muscular response to tetanic nerve stimulation. *Can J Anaesth* 1990; 37:397-400.

(15) Drenck NE, Ueda N, Olsen NV, Engbaek J, Jensen E, Skovgaard LT et al. Manual evaluation of residual curarization using double burst stimulation: a comparison with train-of-four. *Anesthesiology* 1989; 70:578-581.

(16) Fruergaard K, Viby-Mogensen J, Berg H, el Mahdy AM. Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. *Acta Anaesthesiol Scand* 1998; 42:1168-1174.

(17) Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology* 1997; 86:765-771.

ENTROPY

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Entropy has been developed to define the degree of complexity, irregularity, chaos or disorder of a signal. Entropy is an intuitive parameter where one visually distinguishes a regular signal from an irregular one and which is independent of the absolute scales such as the amplitude of the frequency of the signal.

For anaesthesia, the entropy monitoring is based on the acquisition and processing of raw EEG and FEMG signals using the Shannon algorithm (1). The signal is measured by placing a disposable sensor on patient's forehead which allows the recording of the electrical activity of the frontal cortical neurones and the EMG activity of the facial muscles. EEG activity is more regular in sedated than in awake patients and in fact, it is reasonable to assume that the conscious state is dependent of electrical activity of cortical neurones

The General Electric Healthcare Company has developed an Entropy module for the analysis of the frontal EEG which proposes 2 entropy values. The State Entropy (SE) is calculated mainly from EEG and analyses the cortical activity from 0 to 32 Hz (value: 0 to 92). The Response Entropy (RE) is a fast reacting parameter for detecting activation of facial muscles which analyses the electrical activity between 0 and 47 Hz including the EMG activity (value: 0 to 100). A value greater than 90 means that the patient is fully awake. At 40, there is a low probability of consciousness. At 0, there is a suppression of the cortical electrical activity. Individual patients may show different values.

This review will concentrate on the results of the studies using the EEG Entropy algorithm developed by GE and

also on the comparison with the BIS algorithm developed by Aspect Medical.

Vakkuri et al have evaluated the transition from consciousness to unconsciousness in 70 patients during propofol, sevoflurane, and thiopental anaesthesia (2). All indices, RE, SE, and BIS, distinguished excellently between conscious and unconscious states. During regaining of consciousness after a thiopental or propofol bolus, RE and SE values recovered significantly closer to their baseline values than did BIS. Response entropy indicates emergence from anaesthesia earlier than SE or BIS but only 12 sec earlier.

Vanluchene et al have continuously recorded SE, RE and BIS in 10 patients induced by a continuous infusion of propofol at 50 mg/min until either burst suppression was observed during 50% of the time or until mean arterial pressure was below 50 mmHg (3). They also developed pharmacodynamic models relating SE, RE, and BIS to the calculated propofol effect-site concentration (Ceprop). Compared with BIS, both SE and RE seem to be useful electroencephalographic measures of anaesthetic drug effect, with low baseline variability and accurate burst suppression prediction. The ability of the measures to predict Ceprop was best for BIS.

During propofol-remifentanyl anaesthesia the accuracy of SE and RE with the Bispectral Index monitor, Schmidt et al investigated 20 female patients during minor gynaecologic surgery (4). SE, RE, BIS, mean arterial blood pressure, heart rate, and sedation level were recorded every 20 seconds during stepwise increase TCI of 0.5 µg/ml of propofol until the patients lost response followed by a remifentanyl infusion of 0.4 µg.kg(-1).min(-1). SE, RE, and BIS revealed similar information about the level of sedation and allowed the authors to distinguish between different steps of anaesthesia. Both monitors provided useful additional information for the anaesthesiologist.

In 20 unpremedicated patients, the relationship between both BIS and SE values for predicting loss of verbal contact (LVC) and loss of consciousness (LOC) were studied (5). The propofol TCI infusion was set at an initial site-effect concentration of 1 µg.ml-1 and increased by 1 µg.ml-1 steps every 4 min, up to 6.0 µg.ml-1. SE showed a smaller range than BIS and higher correlation with the propofol effect-site concentration. The authors concluded that SE may be more useful than BIS in predicting both LVC and LOC.

The performance of entropy compared with BIS as a measure of anaesthetic effect in different age groups was also studied in fifty-four children receiving a standard sevoflurane anaesthetic for cardiac catheter studies (6). The entropy and BIS were recorded pre-awakening and at 1.5%, 2% and 2.5% steady-state end-tidal sevoflurane

concentrations. For analysis, children were divided into four age groups: 0-1 yr, 1-2 yr, 2-4 yr and 4-12 yr. For both entropy and BIS, the measure of anaesthetic effect was significantly different for children aged less than 1 yr compared with older children. There was no difference in performance of entropy and BIS. Both should be used cautiously in small children.

Even in patients who receive general anaesthesia after good grade subarachnoid haemorrhage BIS and entropy monitoring perform well (7).

If nitrous oxide causes unconsciousness without changing entropy, the addition of nitrous oxide during balanced anaesthesia with sufentanil and sevoflurane provokes a decrease in response and state entropy of the EEG during lumbar disc surgery (8). The authors conclude that SE appears useful to assess the effect of adding N₂O to SEVO during surgery and that such a decrease of SE reflects either an increase in the hypnotic depth or an improvement of analgesia.

The effects of ketamine on BIS, RE and SE during surgery under sevoflurane anaesthesia were also tested in twenty-two women undergoing gynaecological surgery in a double-blind, randomized study (9). Under stable surgical and anaesthetic conditions, a bolus of ketamine 0.5 mg kg⁻¹ causes a significant increase in BIS, RE and SE without modification of the RE-SE gradient. This increase is considered as paradoxical in that it is associated with a deepening level of hypnosis

In patients undergoing laparotomy for inflammatory bowel disease under anaesthesia aimed to maintain BIS between 40 and 60 by isoflurane and nitrous oxide, BIS, RE and SE were measured at each nociceptive stimulation (10). Analgesia was performed by sufentanil bolus administered according to an increase of 20% of systolic blood pressure (SBP) and heart rate compared with the baseline values. In these study conditions, BIS, SE and RE do not allow analgesic requirement evaluation.

The use of BIS or entropy monitoring during anaesthesia has been associated with reduced anaesthetic drug consumption in several studies. In a prospective, randomized, single-blind multicenter study evaluating the effect of entropy monitoring on the consumption of anaesthetic drugs and recovery times after anaesthesia, 368 patients were randomly allocated to anaesthesia with entropy values either shown (target SE: 45 to 65) or not shown (11). Anaesthesia was maintained with propofol, nitrous oxide, and alfentanil which was given to keep the state entropy-response entropy difference below 10 units and heart rate and blood pressure within +/-20% of the baseline values. The control group patients were anaesthetized to keep heart rate and blood pressure within +/-20% of the baseline values. The results show that propofol consumption was smaller in the entropy

group during the whole anaesthesia period and especially during the last 15 min which shortened the time delay in the early recovery parameters in the entropy group.

In a prospective randomized study performed in 140 adult patients scheduled for surgical procedures lasting more than 1 hour, a similar sparing effect of 29% on sevoflurane consumption was demonstrated when sevoflurane anaesthesia technique combined with a fixed sufentanil infusion was controlled by BIS or by spectral entropy compared to a control group using solely the clinical variables for the sevoflurane titration (12).

In a randomized prospective study, we evaluated the entropy sparing effect during long lasting TCI remifentanil-propofol anaesthesia in 90 patients scheduled for major abdominal surgery lasting more than 2 hours (13). Propofol effect-site concentration was adjusted according to the anaesthesiologist's usual TCI practice in the standard group or the conventional 40-60 entropy interval in the entropy group. Remifentanil effect-site concentration was adapted to maintain haemodynamic stability. Propofol consumption was significantly reduced by 17% in the entropy Group.

In conclusion, BIS and Entropy are 2 monitors of the frontal EEG + EMG with a different algorithm. Entropy is a fast simple mathematical method of analysis of the frontal EEG and EMG disorder. BIS-Monitor is a more complex interpretation of frontal EEG + EMG based on a large database of anaesthesia records. BIS and Entropy are not monitors of depth of anaesthesia but there are just indicators of the level of hypnosis. There are no evidence whether these 2 indices differ in performance and in artefact detection but frontal EEG monitoring demonstrates better anaesthesia efficiency such as less drugs utilized and less complications such as prolonged recovery or awareness. In my daily clinical practice, BIS or entropy become standard monitoring when there is a risk of awareness in case of anaesthesia in trauma patients or for caesarean section under general anaesthesia. We also monitor the BIS or entropy in high risk patients, in patients undergoing long lasting surgery and in elderly patients.

However, it is wrong to assume that anaesthesia is a single state reflected by the electrical behaviour of the cerebral frontal cortex and by a figure between 0 and 100 proposed either by the BIS or Entropy monitoring. The patient needs always a good anaesthesiologist knowing the patient and surgery, the surgeon and the limits of the BIS and entropy algorithms. The anaesthetist must always interpret frontal EEG and EMG according to the clinics and the risks of artefacts but without EEG monitoring even as simple as a single frontal probe, the anaesthetist cannot be conscious when the cortex of his patient is inactive.

References:

- 1) Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Meriläinen P. Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiologica Scandinavica* 2004 Feb;48(2):154-61.
- 2) Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, Viertiö-Oja H. Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. *Acta Anaesthesiologica Scandinavica* 2004 Feb;48(2):145-53.
- 3) Vanluchene AL, Vereecke H, Thas O, Mortier EP, Shafer SL, Struys MM. Spectral entropy as an electroencephalographic measure of anesthetic drug effect: a comparison with bispectral index and processed midlatency auditory evoked response. *Anesthesiology*. 2004 Jul;101(1):34-42.
- 4) Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, Schulte Esch J. Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index monitor during propofol-remifentanyl anesthesia. *Anesthesiology*. 2004 Dec;101(6):1283-90.
- 5) Iannuzzi M, Iannuzzi E, Rossi F, Berrino L, Chiefari M. Relationship between bispectral index, electroencephalographic state entropy and effect-site EC50 for propofol at different clinical endpoints. *Br J Anaesth*. 2005 Jul;95(1):117.
- 6) Davidson AJ, Huang GH, Rebmann CS, Ellery C. Performance of entropy and Bispectral Index as measures of anaesthesia effect in children of different ages. *Br J Anaesth*. 2005 Nov;95(5):674-9.
- 7) Duncan D, Kelly KP, Andrews PJ. A comparison of bispectral index and entropy monitoring, in patients undergoing embolization of cerebral artery aneurysms after subarachnoid haemorrhage. *Br J Anaesth*. 2006 May;96(5):590-6.
- 8) Hans P, Dewandre PY, Brichant JF, Bonhomme V. Effects of nitrous oxide on spectral entropy of the EEG during surgery under balanced anaesthesia with sufentanil and sevoflurane. *Acta Anaesthesiol Belg*. 2005;56(1):37-43.
- 9) Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. *Br J Anaesth*. 2005 Mar;94(3):336-40.
- 10) Dierckens E, Fleyfel M, Robin E, Legrand A, Borel M, Gambier L, Vallet B, Lebuffe G. Is entropy a monitor for the guidance of intraoperative analgesia? *Ann Fr Anesth Reanim*. 2007 Feb;26(2):113-8.
- 11) Vakkuri A, Yli-Hankala A, Sandin R, Mustola S, Høymork S, Nyblom S, Talja P, Sampson T, van Gils M, Viertiö-Oja H. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. *Anesthesiology*. 2005 Aug;103(2):274-9.
- 12) Aimé I, Verroust N, Masson-Lefoll C, Taylor G, Laloë PA, Liu N, Fischler M. Does monitoring bispectral index or spectral entropy reduce sevoflurane use? *Anesth Analg*. 2006 Dec;103(6):1469-77.
- 13) Van Rompaey N, Engelman E, Caelen O, Barvais L, Ickx B. Influence of entropy monitoring on drug consumption during and after long lasting TCI anesthesia. Abstract ASA, San Francisco, October 2007.

MONITORING DEPTH OF ANAESTHESIA: BIS

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The Bispectral Index (BIS), calculated from complex mathematical analyses of the cortical electroencephalogram (EEG), correlates with depth of hypnosis and sedation. [1,2] In common with other EEG-based monitors, it cannot indicate the moment of return of consciousness. It does however provide a statistical indication of the likelihood of recall.[3,4] The impact of this on the incidence of awareness has been demonstrated by two large published trials. The first was the “b-aware trial,” [5] a randomised, control trial involving high risk patients in whom the expected incidence of awareness was 1% (as opposed to the overall surgical population in whom the risk is of the order of 0.18% [6]). The trial showed a statistically significant reduction in incidence of awareness with recall, from 0.88% when BIS monitoring was not performed, to only 0.16% when it was performed. A similar 80% reduction in the incidence of awareness was shown in the SAFE2 trial which involved a more general patient population in whom the incidence of awareness in the non-BIS monitored group was 0.18%. [7]

References:

1. Glass PS et al. *Anesthesiology* 1997; 86: 836-847
2. Sebel PS et al. *Anesth Analg* 1997; 84: 891-899
3. Liu J et al. *Anesth Analg* 1997; 84: 185-189
4. Leslie K et al. *Anesth Analg* 1995; 81: 1269-1274
5. Myles PS et al. *Lancet* 2004; 363: 1757-63

6. Sandin RH et al. Lancet 2000; 355: 707-11

7. Ekman A et al. Acta Anaesthesiol Scand 2004; 48: 20-6

CEREBRAL STATE MONITOR (CSM) FOR MONITORING THE ANAESTHETIC STATE

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The traditional depth of anaesthesia (DOA) monitors included formulas for multi-parametric analysis of the electroencephalogram (EEG), with a mathematical function that governs the relationship between EEG parameters and the clinical state of the patient (1).

In order to perform better monitoring conditions in unstable situations the CSM device (Danmeter A/S) has developed a new multi-parametric analysis of the EEG based on the combination of neuronal nets and fuzzy logic (2).

The CSM device measures the hypnotic effect of anaesthetic drugs delivering the Cerebral State Index (CSI), in a dimensionless scale from 0 to 100, being 100 a totally awake and 0 a deeply anesthetized patient. The CSI index is calculated by a fuzzy logic inference system, which consists in a control based method that uses simple rules for rational operation without the use of complex mathematical models. The fuzzy method is an organized mathematical function that is applied to complex processes difficult to simulate, like the EEG. This fuzzy control mode is also utilized for other situations like in some electrical automobile parts, home machines and also in air traffic control(3).

The CSI is calculated based on four validated subparameters of the EEG. The combination of these parameters gives a better performance. The formula which combines the individual EEG parameters is called Adaptive Neuro fuzzy inference system (ANFIS)(4) which automatically selects the best parameter for each clinical condition. If one of them is inadequate other acquires higher impact in the definition of the index.

Previously the ANFIS model was created incorporating to the system signals extracted from 50 patients under anesthesia with different drugs.

The CSM screen displays electromyographic values, burst suppression, signal's quality and the electric impedance for the three electrodes required. Its small size, electric autonomy, portability and its wireless connection option are other advantages of this newer depth of anaesthesia monitor. Different studies have validated the CSM comparing the CSI with clinical endpoints (sedation scale OAA/S), other DOA monitors

or PK parameters like the effect site concentration for propofol (5,6, 7,8,9). All these studies show higher predictability values, for example the correlation coefficient for CSI and BIS is 0.92.(6)

Compared to BIS, CSI has a better performance identifying deeper anesthesia level, allegedly because an earlier correlation with the grade of burst suppression(4). This advantage could be useful for reducing the possibility of delivering high amounts of anaesthetics. CSI has also been evaluated in drugs PK-PD modeling for old and new drugs (6,7,9).

Studies have show different reacting time of the EEG monitors after different speed of induction in laboratories and clinical studies(7,8) but CSI has probably a more rapid response than BIS in fast changes in the anesthetic condition(8).

Discussion: Every new signal incorporated gives us the alternative to focus our clinical management to a specific end point of anaesthesia. Until now, we have the tendency to overestimate the value of EEG information. The anaesthetic effect has been interpreted as a progressive and continuous depression of the CNS, generating high expectation that these DOA monitors would be adequate to reduce overdosing or prevent the risk of awareness, reduce drug consumption drugs and allowing fast tracking patients. All these monitors, even though they can only measure cortical activity, have been proposed (and sold) as "deep of anesthesia monitors"(10).

Nowadays DOA monitors seem to be indicated only for more specific cases like unstable patient, history of drug abuse, trauma, obese or situations when PKPD models are less useful.

It is more reasonable to assume that the anesthetic process is a non linear process.

It is probably more important to pay attention to drug requirements to control the arousal and therefore keeping patients in a adequate level of hypnosis to prevent awareness. The arousal effect activates the thalamo-cortical loops. Loss of consciousness is like a binary process represented in the separation of thalamo-cortical loops at 40Hz (11). Burst suppression is important to prevent overadministration of drugs. The CSM obtains information directly from the patient, therefore having a faster response time and identifying earlier burst suppression compared to other DOA monitors.

1. Kreuer. Acta Anaesth Scand 2004;48:1168-73

2. Smith. Anesthesiology 1996;84: 38-51

3. Jensen. Anesthesiology. 2006;105:28-36

4. Cortinez. Anest Analg 2007;104:605-10

5. Anderson. *EJA* 2006; 23:208–212
6. Zhong. *BJA* 2005 95(6):798-802
7. Sepúlveda. *EJA* 2006; 23(Suppl.37):A-518
8. Pilge. *Anesthesiology* 2006;104:488–94
9. Sepulveda-Cortinez I. Abstract TIVA-TCI World Congress, Venice 2007
10. Task-force report. *Anesthesiology* 2006;104:847-64
11. John. *Anesthesiology* 2005; 102:447-71

IOCVIEW, A NEW MONITOR OF DEPTH OF ANAESTHESIA

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Introduction:

Recent advances in technology and mathematics have facilitated the introduction of more advanced methods in the development of monitors of depth of anaesthesia. The nonlinearity of the EEG justifies the application of complex algorithms in order to extract the state of the brain during general anaesthesia. In this presentation a new monitor for depth of anaesthesia will be presented.

The IoC-view monitor (Morpheus Medical, Barcelona, Spain) has recently been developed and validated in the clinical setting. This monitor calculates a new Index of Consciousness (IoC) based on a chaos mathematical analysis, termed Symbolic Dynamics (SD), of the frontal EEG.

Methods: Symbolic dynamics

The SD is transforming a time series into a symbol sequence which provide a model for the orbits of the dynamical system via a space of sequences. Given a data set X the symbol sequence is achieved by quantizing X into boxes labelled with a symbol. Calculating attributes of the symbol sequence can reveal non-linear characteristics of the EEG. The SD detects the complexity of the EEG which makes it correlate to the depth of anaesthesia.

The IoC-view consists of an amplifier, A/D converter box, and a display. The device is equipped with a Blue-tooth module for communication with PC's, PDAs, mobile phones etc. The IoC view shows the IoC and the auxiliary information such as EEG suppression rate (ESR), electromyogram (EMG), and signal quality as well. The EEG is recorded with three solid hydro-gel surface electrodes.

Results:

The IoC has so far been validated during cardiac anaesthesia using sevoflurane and propofol 1. It has also been validated during sedation for ultrasonographic exploration 2. Comparisons have been made with the Bispectral Index (BIS-XP)[®] (Aspect Medical, Ms,USA) and correlated to the Observers Assessment of Alertness and Sedation Scale (OAAS).

The Pk(SE) values for IoC and BIS with sevoflurane were 0.94(0.04) and 0.84(0.07), respectively 1.

Figure 1 shows the distribution of the IoC versus the OAAS Scale. The IoC shows good agreement with the OAAS scale during induction with sevoflurane. Little overlap was seen between OAAS 5 to 3 (awake levels) and OAAS 2 to 1 (anaesthetised).

Discussion:

The IoC-view is a promising portable new device, characterised by the implementation of an advanced mathematical analysis for assessing the level of consciousness during anaesthesia with sevoflurane or propofol.

References:

- 1 Litvan H, Revuelta ME, Fernández JA, Galan J, Moral V. Comparison of the Index of Consciousness (IoC) and the Bispectral Index during Sevoflurane Anaesthesia. *Anesthesiology* 2006; 105: A1029
- 2 Cortés S, Gambús P. Assessing the level of sedation by the Index of Consciousness (IoC) or the bispectral index (BIS) during ultrasonographic exploration (USE). Spanish Society of Anaesthesia and Reanimation. Valencia, May 2007 Abstract.

SKIN CONDUCTANCE FOR PAIN AND SURGICAL STRESS MONITORING

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Adequate general anaesthesia is a state of sleep or unconsciousness, which is not reversed even by strong surgical, nociceptive stimuli. Whereas adequacy of anaesthetic sleep in a non-stimulated patient may be monitored by EEG parameters, such as BIS, CSM, state entropy or AEP; signs of arousal during surgical stimuli may be difficult to assign to either inadequate hypnotic effect or inadequate analgesia. Changes in blood-pressure and heart-rate is often used as a clinical sign of the balance between analgesic effect and analgesic stimuli, but these parameters are quite unspecific and also subjected to changes in fluid loading, fluid loss and cardiovascular function. Low specificity has also been a problem with other measurement

modalities of physiologic stress, such as muscle tension (EMG, response entropy) or heart rate variability.

Skin conductance is a sensitive and specific monitor of sympathetic output from the central nervous system, as will occur during physiologic stress and pain. The physical bases is an electric current along the skin, which is facilitated when the skin is wet (or sweat) and attenuated when the skin is dry. Each time the sympathetic nerve system is activated a small portion of sweat is released which very rapidly evaporates. A burst, or fluctuation in skin conductance will occur. With strong sympathetic stimulation the number of skin conductance fluctuations (NSCF) and amplitude of each skin conductance fluctuation (ASCF) will increase. With prolonged stimulation the mean level of skin conductance (SC) will also increase, as the evaporation will be insufficient to match the repeated outflow of sweat. With adequate, deep surgical analgesia there will be no release of sweat and the ASCF and NSCF will be zero.

Skin conductance has been shown to evaluate pain response in preterm infants, in intensive care patients and in general anaesthesia. The response is rapid, within few seconds. Skin conductance is not influenced by circulatory changes, by apnoea and respiratory changes, nor by clinical dosing of atropine, beta-blockers or vasoactive drugs. However, in the fully awake patient skin conductance is fairly unspecific, as sweating is highly influenced by emotional state as well as by nociception.

So far in clinical studies, skin conduction seems to be more sensitive to surgical stress or intubation stress than BIS or entropy, with a good correlation to epinephrine levels and clinical signs of stress. It is also possible that the different skin-conductance parameters may be used to distinguish between stress due to inadequate hypnotic effect versus stress due to inadequate analgesic effect.

References:

- Goddard GF. *Anaesthesia* 1982;37:408 (første med anesthesi)
- Bengtsson M et al. *Acta Anaesthesiol Scand* 1985;29:67-71 (spinal an)
- Storm H. *Arch Dis Child Fetal Neonatal Ed.* 2000; 83:F-143-7
- Storm H et al. *Acta Anaesthesiol Scand* 2002;46:887-95. (første hanne m/ anaesthesia)
- Storm H et al. *Acta Anaesthesiol Scand* 2005; 49:798-803. (NSCF bedre enn BIS)
- Ledowski T et al. *Br J Anaesth* 2006;97:817-21. (Bis bedre på oppvåkning, men tregere)

Gjerstad AC et al. *Acta Anaesthesiol Scand* 2007; 51:8-15. (NSCF bedre enn entropy)

EVALUATION OF CONSTANT PLASMA EQUILIBRIUM - EFFECT SITE (KE0) AND PROPOFOL: COMPARISON OF BIS - AEP IN CHILDREN

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Background. The plasma effect site equilibration rate constant (ke_0) describes the removal of the drugs from the effect site. This parameter, in conjunction with an appropriate set of pharmacokinetic parameters allows targeting the effect site or predicting the effect site concentrations after manual dosing scheme. The plasma effect site kinetics for propofol in children have been at the moment not well characterised. As there are pharmacodynamic differences between adults and children, it is not correct to use in children the plasma effect site kinetics calculated for adults. The two most popular paediatric sets of pharmacokinetic parameters for propofol are those of Kataria, for children aged 3-11 years, and the set used in the "Paedfusor", for children aged 1-16 years. None of these sets incorporates the plasma effect site kinetics. The study of Munoz (1) estimated the ke_0 for this two pharmacokinetic models using the time to peak effect (t_{peak}) method, employing the auditory evoked potentials (AEP) as measure of the effect, but this monitor is not validated for the use in children. No studies at the moment have been performed in children using the bispectral index (BIS). It has been suggested that different methods of measure of the effect of anaesthetic drugs represent different aspects of the cerebral activity, and it is possible that different measuring methods provide different rate of equilibration with plasma, in relation to different sites of action in the central nervous system. The aim of this study was to evaluate the plasma effect site equilibration for propofol in children using the method of t_{peak} , comparing two methods of measure of the effect: BIS and AEP. We could also calculate from the t_{peak} values the ke_0 for the pharmacokinetic set of Kataria and for the set of the "Paedfusor", using the method described by Minto (2). **Methods.** After informed consent 43 children aged 3-11 years with ASA physical status I or II were studied. All patients were unpremedicated. Randomly 22 patients were assigned to the BIS group (A-2000 BIS monitor version XP) and 21 to the AEP group (A-Line AEP monitor). A submaximal bolus dose of propofol 1%, ranging from 1,5 to 2 mg/kg was injected manually in all patients and the BIS and AEP values were recorded every second for subsequently determination of the t_{peak} . For each patient was then

calculated the ke0 value for the set of Kataria and for the set of the "Paedfusor". For validation, the median value of ke0 of both groups was tested calculating the prediction error (PE) with the formula: $t_{peak\ measured} - t_{peak\ predicted} / t_{peak\ predicted} * 100$.

The performance of the population ke0 was expressed in terms of bias (median PE, MDPE) and precision (median absolute PE, MDAPE). Results: In the BIS group the mean tpeak value was 63 ± 16 s and in the AEP group was 145 ± 45 s ($p < 0,001$). The median ke0 calculated for the set of Kataria was 2,25 min⁻¹ (range 0,78 - 4,54) in the BIS group (MDPE = 3,5, MDAPE = 10,6) and 0,65 min⁻¹ (range 0,23 - 3,28) in the AEP group (MDPE = 0, MDAPE = 14,6). The median ke0 calculated for the set of the "Paedfusor" was 2,69 min⁻¹ (range 1,01 - 5,22) in the BIS group (MDPE = 0, MDAPE = 11,2) and 0,85 min⁻¹ (range 0,26 - 3,79) in the AEP group (MDPE = 0, MDAPE = 16,4). Conclusions: In the paediatric patients the peak of the effect of a submaximal bolus of propofol measured with BIS is reached earlier than that measured with AEP. This suggests the hypothesis that these two monitors measure the effect of propofol on different sites of action, that have different rates of equilibration with plasma.

References:

1. Muñoz HR, Cortinez LI, Ibacache ME, Altermatt FR. Estimation of the plasma effect site equilibration rate constant (ke0) of propofol in children using the time to peak effect. *Anesthesiology* 2004;101:1269 – 74
2. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003;99:324 – 33

REMIFENTANIL AND DESFLURANE: A NEW KIND OF BALANCED ANAESTHESIA

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Background: T.C.I. with propofol and remifentanyl is the most used anaesthetic technique in our Institution. It is particularly effective in improving the control of the surgical field bleeding, and this characteristic is very useful in E.N.T. (ear, nose and throat) surgery (1, 2, 3, 4, 5).

This observational study was performed in 30 patients with American Society of Anesthesiologists physical status I or II, aged 20–65 yr, undergoing microscopic and endoscopic sinus surgery. The aim was to test the hypothesis that a balanced anaesthesia technique using

Desflurane-Remifentanyl combination, when compared with intravenous anaesthesia with Propofol-Remifentanyl, offers the same advantages in this type of surgery: a stable anaesthesia, easy changing of the depth of anaesthesia, easy control of bleeding by means of controlled hypotension achieved through the anaesthetic drugs, and a rapid wake-up after surgery.

Desflurane-Remifentanyl combination has been recommended as an optimal way of maintaining anaesthesia because of its rapid onset and fast elimination, improved haemodynamic stability and allowing both rapid adjustments of the depth of anaesthesia through intraoperative titration and rapid recovery (6, 7, 8, 9).

Both Remifentanyl and Desflurane are characterized by very fast pharmacokinetics, but these two drugs cannot be used alone or together to induce the anaesthesia, because Desflurane is an irritant for the airways and for this reason it is not tolerated by patients when breathing spontaneously (10, 11); Remifentanyl is not a hypnotic drug able to induce anaesthesia, therefore it needs to be used together with a hypnotic in order to avoid awareness and muscular rigidity as side effects.

Propofol is a generally well tolerated anaesthetic agent with a low incidence of allergic adverse reactions. However, there have been scattered reports of apparently allergic reactions: 1.2% of cases of peri-operative anaphylactic shock in France are attributable to allergy to Propofol (diisopropylphenol, soybean oil, egg lecithin and glycerol) (12). When Propofol Injectable Emulsion couldn't be used in patients with a known hypersensitivity to one of its components, we induced hypnosis with Thiopental Sodium combined with Remifentanyl and

Mivacurium, and maintained anaesthesia with Desflurane-Remifentanyl combination.

The aims of this observational study were:

- to assess the quality of anaesthesia for E.N.T. surgery while using the combination Desflurane – Remifentanyl, compared to T.I.V.A. by the combination Propofol - Remifentanyl, and

- to determine which kind of combination of these two drugs (Desflurane and Remifentanyl) is optimal to obtain the best from both of them, whether keeping constant the concentration of one of them and variable the other, or vice versa.

Methods (Study Protocol):

We randomly assigned 30 healthy adult patients undergoing E.N.T. surgery (microscopic and endoscopic sinus surgery) to one of three groups: PR (Propofol - Remifentanyl), Rc+Dv (Remifentanyl constant and

Desflurane variable) and Rv+Dc (Remifentanyl variable and Desflurane constant).

Premedication:

In all groups we used Midazolam 0.02 mg/Kg e.v.

Induction:

In all groups after breathing 100% oxygen for 3 min, anaesthesia was induced by titrating effect site target concentration of Propofol (Schnider's model) and Remifentanyl (Minto's model), to reach a BIS value between 30-40 and a 20-40 % reduction of preoperative mean systolic blood pressure, defined as the mean of three systolic blood pressures measured since admission.

When patients did respond to the laryngoscopy, the target remifentanyl concentration was increased by 2-4 ng/ml, depending on the intensity of the response, for the following laryngoscopy. When the new effect site target remifentanyl concentration was reached, the following laryngoscopy was performed.

Responses to laryngoscopy was defined using the same criteria as used to define inadequate anaesthesia, by the following criteria (13, 14):

1. An increase in systolic blood pressure by more than 15 mmHg above the preoperative mean systolic blood pressure
2. A heart rate exceeding 90 beats/min in the absence of hypovolemia
3. Other autonomic signs such as sweating or flushing
4. Somatic responses such as movements or swallowing

In case of adverse events during induction or maintenance of anaesthesia, the reactions were the following:

- (relative) Hypertension (Systolic blood pressure >90 mmHg):

Note BIS:

if BIS >40, optimize BIS: increase target propofol concentration 10%;

if BIS <40, optimize analgesia: increase target remifentanyl concentration 20% .

- Hypotension (Systolic blood pressure <80 mmHg)

Note BIS:

if BIS >40, use vasopressor (ephedrine 5 mg) and/or plasma expander 5 ml/Kg rapid infusion (Hydroxyethyl Starch, HES 130/0.4);

if BIS <40, decrease propofol target concentration 20% and use vasopressor and/or plasma expander if required.

- Tachycardia (HR >90 beats/min)

Note BIS:

if BIS >40, optimize BIS: increase target propofol concentration 10% and, if indicated, optimize analgesia: increase target remifentanyl concentration 20%;

if BIS <40, administer metoprolol 1-2 mg.

- Bradycardia (HR <40 beats/min)

Administer atropine 0.01 mg/Kg.

- Myocardial ischaemia (ST-segment depression >1 mm)

Optimize patient haemodynamics and ventilation:

if HR >60, administer metoprolol 1-2 mg;

if HR <60, administer GTN (glyceryl trinitrate) infusion 10-100 mg/min.

Patient movement:

Note BIS and increase target propofol concentration 20%.

Patients with a known hypersensitivity to Propofol Injectable Emulsion or its components were induced by Thiopental Sodium combined with Remifentanyl, and randomly assigned to one of the two groups in which maintenance was assured by the combination of Desflurane and Remifentanyl (Rc+Dv or Rv+Dc).

Mivacurium 0,15 mg/Kg was given as neuromuscular blocker when necessary to facilitate tracheal intubation.

All patients received lactated Ringers' at approximately 15 ml/kg before/during the induction and were placed in a 5° reverse Trendelburg position to improve venous drainage.

Once intubation was complete, ventilation was guaranteed by an automatic respirator providing a mixture of air and oxygen at 40%.

Maintenance:

Group PR (n=10): after the tracheal intubation the target propofol concentration was modified during the surgical procedure to maintain optimal values of BIS (30-40) and finally discontinued at the end of the procedure. The remifentanyl administration was changed in response to the presence or absence of signs of inadequate anaesthesia. When signs of inadequate anaesthesia developed, the target remifentanyl concentration was modified by 1-10 ng/ml.

Group Rc+Dv (n=10): after tracheal intubation the remifentanyl administration was continued to a constant effect site target of 6 ng/ml till the end of the procedure, and Propofol infusion was discontinued, replaced by Desflurane at a variable concentration (minimum end tidal concentration 3%) in response to the presence or absence of signs of inadequate anaesthesia. When signs

of inadequate anaesthesia developed, the Desflurane concentration was modified by 10-20%.

In case of adverse events during maintenance of anaesthesia, the reactions were the following:

- (relative) Hypertension (Systolic blood pressure >90 mmHg): increase Desflurane concentration by 1%
- Hypotension (Systolic blood pressure <80 mmHg):

Note BIS:

if BIS >40, use vasopressor (ephedrine 5 mg) and/or plasma expander 5 ml/Kg rapid infusion (Hydroxyethyl Starch, HES 130/0.4);

if BIS <40, decrease Desflurane concentration by 1% (minimum end tidal concentration 3%) and use vasopressor and/or plasma expander if required.

- Tachycardia (HR >90 beats/min)

Note BIS:

if BIS >40, optimize BIS: increase Desflurane concentration by 1%,

if BIS <40, administer metoprolol 1–2 mg.

- Bradycardia (HR <40 beats/min)

Administer atropine 0.01 mg/Kg.

- Myocardial ischaemia (ST-segment depression >1 mm)

Optimize patient haemodynamics and ventilation:

if HR >60, administer metoprolol 1–2 mg;

if HR <60, administer GTN (glyceryl trinitrate) infusion 10–100 mg/min.

- Patient movement

Note BIS and increase Desflurane concentration by 1%.

Group Rv+Dc (n=10): after tracheal intubation Propofol infusion was discontinued, replaced by Desflurane at a constant end tidal concentration of 5% till the end of the procedure; Remifentanyl administration was continued to a variable effect site target in response to the presence or absence of signs of inadequate anaesthesia. When signs of inadequate anaesthesia developed, the Remifentanyl concentration was modified by 10-20%.

In case of adverse events during maintenance of anaesthesia, the reactions were the following:

- (relative) Hypertension (Systolic blood pressure >90 mmHg): increase Remifentanyl effect site target concentration by 10-20%
- Hypotension (Systolic blood pressure <80 mmHg):

Note BIS:

if BIS >40, use vasopressor (ephedrine 5 mg) and/or plasma expander 5 ml/Kg rapid infusion (Hydroxyethyl Starch, HES 130/0.4);

if BIS <40, decrease Remifentanyl effect site target concentration by 10-20% and use vasopressor and/or plasma expander if required.

- Tachycardia (HR >90 beats/min)

Note BIS:

if BIS >40, optimize BIS: increase decrease Remifentanyl effect site target concentration by 10-20%

if BIS <40, administer metoprolol 1–2 mg.

- Bradycardia (HR <40 beats/min)

Administer atropine 0.01 mg/Kg.

- Myocardial ischaemia (ST-segment depression >1 mm)

Optimize patient haemodynamics and ventilation:

if HR >60, administer metoprolol 1–2 mg;

if HR <60, administer GTN (glyceryl trinitrate) infusion 10–100 mg/min.

- Patient movement

Note BIS and increase Remifentanyl effect site target concentration by 20%.

In all groups the variable drug requirements were adjusted to both BIS and haemodynamics, having as a target a MBP of 60-70 mmHg, a systolic blood pressure between 80-90 mmHg and a heart rate of minimum 45 BPM, to limit bleeding in the surgical field. Anaesthetic depth was adjusted to a BIS of 30-40.

We measured the variations of the cardiovascular parameters during the whole procedure in order to evaluate the quality of the results obtained, and the time to wake up once the delivery of the drugs had finished.

Thirty minutes before the end of surgery, 1 mg/Kg intravenous tramadol was injected to provide relief of (moderate) post-operative pain.

At the end of surgery the administration of the drugs was discontinued, and neuromuscular blockade was antagonized by neostigmine, 1–2 mg intravenously, and atropine 0.5–1 mg intravenously, when necessary.

Emergence:

In all groups the patients were tested every 2 minutes by verbal commands to evaluate return of consciousness.

This was defined as a positive response to a verbal command, confirmed by BIS values of 80 or higher(15). Once adequate spontaneous ventilation was established (i.e., if the end-tidal carbon dioxide partial pressure was less than 46 mmHg, tidal volume was more than 7

ml/kg, respiratory rate was more than 10 breaths/min.), the trachea was extubated, and the time from the end of surgery till extubation recorded.

Immediately after tracheal extubation, the patient was asked to declare the date of birth, to test postoperative cognitive and psychomotor recovery from anaesthesia.

Results (preliminary data):

Cardiovascular stability. We noted that cardiovascular stability was assured in an optimal way by all the three methods of maintaining anaesthesia: after a drop of 30-35% of both MAP and heart rate at the induction, the cardiovascular values remained stable till the end of surgery in any case. It was never necessary to deliver anti cholinergic drugs or sympathomimetic drugs to react to hypotension.

Time to extubation. The times from the end of surgery to tracheal extubation and the times until leaving the operating room were not significantly different between the three groups (mean time to extubation, Group Rv+Dc = 12,6 minutes; Group Rc+Dv = 10,5 minutes; Group PR = 12,4 minutes.

Orientation and response to commands (date of birth) after extubation. All the patients were able to declare their date of birth immediately after extubation.

We noted that it was easier to modify the depth of anaesthesia if necessary to react to the clinical responses of the patients receiving Desflurane when this drug was kept constant and the effect site Remifentanil target was modified, as compared to the other mode, when the target of Remifentanil was constant and the concentration of Desflurane was modified.

The reason for this is probably related to the necessity to pass from semi-closed circuit to open circuit ventilation in order to accelerate the modification of the concentration of Desflurane, which requires a slightly longer time to reach the new level of anaesthesia desired if compared with the time necessary to obtain it by changing the effect site target of Remifentanil.

Conclusions:

The combination of Remifentanil and Desflurane is an optimal way of delivering anaesthesia to patients undergoing microscopic and endoscopic sinus surgery.

Cardiovascular stability, controlled hypotension maintained by the same drugs used for anaesthesia, rapidity and quality of the emergence are comparable when Desflurane – Remifentanil or Propofol - Remifentanil combinations are used.

It seems to be easier to adapt the depth of anaesthesia to the needs of patients and surgeons in the different phases of surgical procedures when the concentration of Desflurane administered is maintained constant (end

tidal 5%) and the target of Remifentanil is modified, rather than vice versa.

It could be necessary to improve the number of patients involved in the study to discover if one of the drug combinations proposed in this study presents advantages when compared to the others.

References:

1. Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. *Laryngoscope*. 2003 Aug;113(8):1369-73.
2. Tirelli G, Bigarini S, Russolo M, Lucangelo U, Gullo A. Total intravenous anaesthesia in endoscopic sinus-nasal surgery. *Acta Otorhinolaryngol Ital*. 2004 Jun;24(3):137-44.
3. Blackwell KE, Ross DA, Kapur P, Calcaterra TC. Propofol for maintenance of general anesthesia a technique to limit blood loss during endoscopic sinus surgery. *Am J Otolaryngol*. 1993 Jul-Aug;14(4):262-6.
4. Pavlin JD, Colley PS, Weymuller EA, Van Norman G, Gunn HC, Koerschgen ME. Propofol versus isoflurane for endoscopic sinus surgery. *Am J Otolaryngol*. 1999 Mar-Apr;20(2):96-101.
5. Sivaci R, Yilmaz MD, Balci C, Erincler T, Unlu H. Comparison of propofol and sevoflurane anesthesia by means of blood loss during endoscopic sinus surgery. *Saudi Med J*. 2004 Dec;25(12):1995-8.
6. Eberhart LH, Kussin A, Arndt C, Lange H, Folz BJ, Werner JA, Wulf H, Kill C. Effect of a balanced anaesthetic technique using desflurane and remifentanil on surgical conditions during microscopic and endoscopic sinus surgery. *Rhinology*. 2007 Mar;45(1):72-8.
7. Grottko O, Dietrich PJ, Wiegels S, Wappler F. Intraoperative Wake-Up Test and Postoperative Emergence in Patients Undergoing Spinal Surgery: A Comparison of Intravenous and Inhaled Anesthetic Techniques Using Short-Acting Anesthetics. *Anesth Analg* 2004;99:1521-1527.
8. Mustafa Cengiz, Suleyman Ganidagli, Alper Sami Kunt, Osman Tansel Darcin. Propofol-Remifentanil Induction Followed By Desflurane-Remifentanil Anaesthesia Without Muscle Relaxant In Patients With Myasthenia Gravis For Thymectomy. *The Internet Journal of Anesthesiology*. 2005. Volume 9 Number 1.
9. Billard V, Servin F, Guignard B, Junke E, Bouverne MN, Hédouin M, Chauvin M (2004) Desflurane-remifentanil-nitrous oxide anaesthesia for abdominal surgery: optimal concentrations and recovery features. *Acta Anaesthesiologica Scandinavica* 48 (3), 355–364.

10. Olsson G. L (1995) Inhalational anaesthesia at the extremes of age: paediatric anaesthesia *Anaesthesia* 50 (s10), 34–36.
11. Wilkes AR, Raj N, Hall JE. Adverse airway events during brief nasal inhalations of volatile anaesthetics: the effect of humidity and repeated exposure on incidence in volunteers preselected by response to desflurane. *Anaesthesia*. 58(3):207-216, March 2003.
12. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and Anaphylactoid Reactions Occurring during Anesthesia in France in 1999–2000. *Anesthesiology* 2003; 99:536–45.
13. Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. *Anesthesiology* 1995; 83:8–22.
14. Mertens MJ, Olofsen E, Engbers FH M, Burm AGL, Bovill JG, Vuyk J. Propofol Reduces Perioperative Remifentanil Requirements in a Synergistic Manner. Response Surface Modeling of Perioperative Remifentanil–Propofol Interactions. *Anesthesiology* 2003; 99:347–59.
15. Bruhn J, Kreuer S, Bischoff P, Kessler P, Schmidt GN, Grzesiakl A, Wilhelm W. Bispectral index and A-line AAI index as guidance for desflurane-remifentanil anaesthesia compared with a standard practice group: a multicentre study. *British Journal of Anaesthesia* 2005 94(1):63-69.

REMIFENTANIL AND DESFLURANE: A GOOD COMBINATION FOR CARDIAC PROTECTION

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In the last recent years there has been an increasing interest in the literature in the evaluation the effectiveness of anaesthetics in protecting the heart against myocardial ischemia-reperfusion injury.

Protection by several anaesthetics is relatively well investigated. It is generally agreed that some anaesthetic agents reduce the myocardial damage caused by ischemia and reperfusion. Although clinical applicability of anesthetic agent-induced protection has yet to be established, there is increasing evidence of anesthetic agent induced protection. At present volatile anaesthetics and opioids appear to be most promising as preconditioning-inducing agents.

There are some proposed mechanisms for protection by anesthetic agents, but ischemic preconditioning-like effect seems to be mainly involved. Ischemic

preconditioning initially referred to the ability to reduce myocardium infarct size. In the last years the definition has been extended to include other endpoints, such as stunning and coronary abnormalities. In humans, ischemic preconditioning reduces troponin release, enhances post-ischemic contraction in ventricular trabeculae muscle, and improves survival rate of isolated cardiomyocytes. This means that ischemic preconditioning is able to interfere with ischemia, stunning and reperfusion damage.

Ischemic stimuli cause the release of stress mediators from the heart, including adenosine, bradykinin, opioids, noradrenaline and free radicals. Such substances act as initiators by passing signals to intracellular components, such as inhibitory guanine nucleotide binding proteins (Gi proteins) and protein kinase C (PKC). ATP-sensitive K⁺ channels (KATP channels) on the sarcolemma and mitochondria are activated. Recent studies support the theory that mitochondrial KATP channels play a greater role than sarcolemmal KATP channels. Blockade of the identified mediators involved in ischemic preconditioning reverses the protective effect both in experimental and clinical settings.

Experimental findings indicate that the signals for anaesthetics, like for brief ischemia in ischemic preconditioning, are preserved in intracellular components that can mediate protection against ischemia. The protection by halogenated anesthetics has been reversed by selective adenosine A₁ receptor antagonist, Gi protein inhibitor, PKC inhibitors, and KATP channel blockers. Contribution of the mitochondrial KATP channel appears certain, whereas there is still some doubt about the sarcolemmal KATP channel. These observations strongly suggest that halogenated anesthetic agents provide protection via a mechanism similar to that of ischemic preconditioning. Hence, it can be assumed that the halogenated anesthetics stimulate adenosine receptors, followed by Gi proteins, PKC and KATP channels. As the protection by halogenated anesthetics is not accompanied by augmented release of adenosine, it could be assumed that they stimulate adenosine receptors via a non-adenosine mechanism, or upregulate the adenosine receptor-G protein.

The involvement of opioid receptors in ischemic preconditioning has been demonstrated in various experiments in animals and humans. Among opioid receptor subtypes, there is evidence that K and Δ-opioid receptors are responsible for ischemic preconditioning. Although opioid receptors are more abundant in the central nervous system, they are also present in the heart. Opioid receptor subtype distribution in the heart appears to differ between species. K and Δ-opioid receptors, but not μ-opioid receptors are expressed in the heart. In human atrium, K and μ- have

been shown to be dominant compared to Δ -receptors. Naloxone showed to block the effect of ischemic preconditioning in isolated hearts, cardiac myocytes and in in vivo models. Therefore it is suggested that it is in the heart itself that opioid receptors play a role in protection by ischemic preconditioning. There is evidence that exogenous opioids precondition the heart. Administration of remifentanyl to the heart also reduced myocardial infarct/injury induced subsequently by ischemia and reperfusion, indicating cardioprotection. The cardioprotection can be abolished with blockade of K or Δ but not μ -receptors. This is experimental evidence that remifentanyl also confers cardioprotection via cardiac K- and Δ -receptors. In addition, it is reported that the cardioprotection by opioids and ischemic preconditioning share the same signaling mechanisms, namely PKC and mito-KATP channels.

An increasing number of investigations demonstrate that halogenated anesthetics and opioids protect against myocardial ischemia-reperfusion injury. Currently halogenated anesthetics are the most promising agents as cardioprotectors among anesthetics. Their beneficial effects against ischemia-reperfusion injury have been demonstrated better than for any other anesthetic. In addition halogenated anesthetics confer protection at clinically relevant concentrations.

Opioids, namely morphine and remifentanyl, have also been shown to be protective at clinical concentrations.

The effect of halogenated anesthetics and morphine or remifentanyl, when they are given after the onset of ischemia, remains questionable, although some evidence of postconditioning effect is reported.

At moment, the evidence in experimental and clinical settings suggests that halogenated and opioid drugs are able to mitigate myocardial injury during ischemia. Then, halogenated anesthetics and opioids might be good combination in anesthetizing patients with or at risk of myocardial ischemia.

References:

1. De Hert SG: The concept of anaesthetic-induced cardioprotection: Clinical relevance. *Best Pract Res Clin Anaesthesiol* 19:445-459, 2005
2. De Hert SG, Turani F, Mathur S, et al: Cardioprotection with volatile anesthetics: Mechanisms and clinical implications. *Anesth Analg* 100:1584-1593, 2005
3. Weber NC, Schlack W: The concept of anaesthetic-induced cardioprotection: Mechanisms of action. *Best Pract Res Clin Anaesthesiol* 19:429-443, 2005

4. Zaugg M, Schaub MC, Foex P: Myocardial injury and its prevention in the perioperative setting. *Br J Anaesth* 93:21-33, 2004
5. Kato R, Foex P: Myocardial protection by anaesthetic agents against ischemia-reperfusion injury: An update for anesthesiologists. *Can J Anaesth* 49:777-791, 2002
6. Riess ML, Stowe DF, Warltier DC: Cardiac pharmacological preconditioning with volatile anesthetics: From bench to bedside? *Am J Physiol Heart Circ Physiol* 286:H1603-1607, 2004
7. Cohen G, Shirai T, Weisel RD, et al: Optimal myocardial preconditioning in a human model of ischemia and reperfusion. *Circulation* 98:II184-II196, 1998
8. De Hert SG, Van der Linden PJ, et al: Choice of primary anaesthetic regimen can influence intensive care unit length of stay in coronary surgery with cardiopulmonary bypass. *Anesthesiology* 101:9-20, 2004
9. De Hert SG, Van der Linden PJ, Cromheecke S, et al: Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* 101:299-310, 2004
10. Guarracino F, Landoni G, Tritapepe L, et al. Myocardial damage prevented by volatile anesthetics: a multicentre randomized controlled study. *J Cardiothor Vasc Anesth* 20; 477-483, 2006
11. Tritapepe L, Landoni G, Guarracino F, et al. Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *Eur J Anaesthesiol* 2007 Apr;24(4):323-31
12. Landoni G, Biondi-Zoccai GL, Zangrillo A et al.: Desflurane and Sevoflurane in Cardiac Surgery: A Meta-Analysis of Randomized Clinical Trials. *Journal of Cardiothoracic and Vascular Anesthesia*. 2007 (in press)
13. Zhang Y, Irwin MG, Wong TM: Remifentanyl preconditioning protects against ischemic injury in the intact rat heart. *Anesthesiology* 2004; 101:918-23
14. Ventura C, Bastagli L, Bernardi P, Caldarera CM, Guarnieri C: Opioid receptors in rat cardiac sarcolemma: Effect of phenylephrine and isoproterenol. *Biochim Biophys Acta* 1989; 987:69-74
15. Tai KK, Jin WQ, Chan TK, Wong TM: Characterization of [³H]U69593 binding sites in the rat heart by receptor binding assays. *J Mol Cell Cardiol* 1991;23:1297-302

16. Zhang WM, Jin WQ, Wong TM: Multiplicity of kappa opioid receptor binding in the rat cardiac sarcolemma. *J Mol Cell Cardiol* 1996; 28:1547-54
17. Krumins SA, Faden AI, Feuerstein G: Opiate binding in rat hearts: Modulation of binding after hemorrhagic shock. *Biochem Biophys Res Commun* 1985;127:120-8
18. Wong TM, Lee AY, Tai KK: Effects of drugs interacting with opioid receptors during normal perfusion or ischemia and reperfusion in the isolated rat heart: An attempt to identify cardiac opioid receptor subtype(s) involved in arrhythmogenesis. *J Mol Cell Cardiol* 1990; 22:1167-75
19. Ventura C, Spurgeon H, Lakatta EG, Guarnieri C, Capogrossi MC: Kappa and delta opioid receptor stimulation affects cardiac myocyte function and Ca²⁺ release from an intracellular pool in myocytes and neurons. *Circ Res* 1992;70:66-81
20. Ela C, Barg J, Vogel Z, Hasin Y, Eilam Y: Distinct components of morphine effects on cardiac myocytes are mediated by the kappa and delta opioid receptors. *J Mol Cell Cardiol* 1997; 29:711-20
21. James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ: Opioid receptor activity of GI 87084B, a novel ultra-short acting analgesic, in isolated tissues. *J Pharmacol Exp Ther* 1991; 259:712-8
22. Fryer RM, Hsu AK, Nagase H, Gross GJ: Opioid-induced cardioprotection against myocardial infarction and arrhythmias: Mitochondrial versus sarcolemmal ATP-sensitive potassium channels. *J Pharmacol Exp Ther* 2000; 294:451-7
23. Fryer RM, Pratt PF, Hsu AK, Gross GJ: Differential activation of extracellular signal regulated kinase isoforms in preconditioning and opioid-induced cardioprotection. *J Pharmacol Exp Ther* 2001; 296:642-9
24. Fryer RM, Wang Y, Hsu AK, Gross GJ: Essential activation of PKC-delta in opioid-initiated cardioprotection. *Am J Physiol Heart Circ Physiol* 2001; 280: H1346-53
25. Fryer RM, Pratt PF, Hsu AK, Gross GJ: Differential activation of extracellular signal regulated kinase isoforms in preconditioning and opioid-induced cardioprotection. *J Pharmacol Exp Ther* 2001; 296:642-9
26. Wang GY, Wu S, Pei JM, Yu XC, Wong TM: Kappa- but not delta-opioid receptors mediate effects of ischemic preconditioning on both infarct and arrhythmia in rats. *Am J Physiol Heart Circ Physiol* 2001; 280:H384-91

IS POSTOPERATIVE CHRONIC PAIN PREVENTABLE?

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The occurrence of postoperative chronic pain is linked to various factors. Some of these cannot be influenced by the intervention of anesthesiologists (patient psychological status, hereditary factors.....), but some in particular the quality of the postoperative pain treatment may have a beneficial effect to prevent or lower the occurrence of the postoperative chronic pain syndrome.

Chronic pain after surgery is not a new syndrome, but this question has only been addressed in recent reviews(1). Typically, preoperative pain-free patients experience a pro-longation of postoperative pain that persists during at least 3 months without relapse or pain-free interval. Chronic pain syndromes have been described after breast surgery, hernia repair, cholecystectomy, thoracic surgery, and limb or organ amputation(1). Almost 5% of patients who have undergone hernia repair complain of severe pain 1 year after surgery(2). In patients having thoracotomy, the incidence of a chronic pain syndrome is as high as 60% at 6 months after surgery(3). After breast surgery, different kinds of pain syndromes have been described, such as phantom pain and postmastectomy syndrome(4).

Risk factors are difficult to identify, but patients who experience severe pain and above all, persistence of postoperative pain several days after the expected duration, are prone to develop a chronic pain syndrome(5,6). On the basis of this it was worth trying to demonstrate that efficient postoperative pain control could prevent the occurrence of chronic pain syndromes. This was demonstrated in thoracic surgery, where epidural analgesia compared to intravenous PCA morphine tends to reduce the incidence of chronic pain syndrome(7).

Another approach consists in drugs that may prevent the occurrence of allodynia and hyperalgesia postoperatively. Indeed, during surgery tissue damage induces release of free fatty acids and cytokines and induction of cyclo-oxygenase-2 that results in prostaglandin synthesis(8). Prostaglandins are thought to promote transmission of nociceptive stimulation both at nerve endings and at the level of the dorsal horn of spinal cord(9). A complex sensitization phenomenon is responsible for allodynia and hyperalgesia that is documented after surgery. Ketamine used in low doses (0.1-0.5 mg/kg) can block NMDA re-ceptors. Postoperative administration of ketamine has been documented to not only reduce opioid consumption and improve postoperative pain control but also lower the incidence of chronic pain syndromes(10). Other

analgesic agents could potentially reduce or prevent postoperative hyperalgesia and consequently could avoid the occurrence of chronic pain. Among these drugs α_2 -adrenergic agents(11), COXibs and local anesthetic agents that have been demonstrated to prevent inflammatory processes after tissue damage(12,13). The administration of gabapentin decreases postoperative opioid consumption when given at the time of anaesthetic induction(14). Promising results have been obtained in the reduction of chronic pain after breast surgery with gabapentin, EMLA, and a combination of the two, but also with venlafaxine, a tricyclic antidepressant(15).

References:

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618-25.
2. Callesen T, Kehlet H. Postherniorrhaphy pain. *Anesthesiology* 1997;87:1219-30.
3. Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiol Scand* 1999;43:563-7.
4. Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: a survey of 282 women. *Pain* 1996;66:195-205.
5. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. *Clin J Pain* 1996;12:50-5.
6. Haythornthwaite JA, Raja SN, Fisher B et al. Pain and quality of life following radical retropubic prostatectomy. *J Urol* 1998;160:1761-4.
7. Senturk M, Ozcan PE, Talu GK et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002;94:11-5.
8. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 2001;294:1871-5.
9. Samad TA, Moore KA, Sapirstein A et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 2001;410:471-5.
10. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? *Pain* 2001;92:373-80.
11. Lavand'homme PM, Eisenach JC. Perioperative administration of the alpha2-adrenoceptor agonist clonidine at the site of nerve injury reduces the development of mechanical hypersensitivity and modulates local cytokine expression. *Pain* 2003;105:247-54.

12. Beloeil H, Ji RR, Berde CB. Effects of bupivacaine and tetrodotoxin on carrageenan-induced hind paw inflammation in rats (Part 2): cytokines and p38 mitogen-activated protein kinases in dorsal root ganglia and spinal cord. *Anesthesiology* 2006;105:139-45.

13. Beloeil H, Ababneh Z, Chung R et al. Effects of bupivacaine and tetrodotoxin on carrageenan-induced hind paw inflammation in rats (Part 1): hyperalgesia, edema, and systemic cytokines. *Anesthesiology* 2006;105:128-38.

14. Hurley RW, Cohen SP, Williams KA et al. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med* 2006;31:237-47.

15. Fassoulaki A, Triga A, Melemini A, Sarantopoulos C. Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesth Analg* 2005;101:1427-32.

MONITORING COGNITIVE FUNCTIONS FOLLOWING TIVA-TCI AND INTEGRATED TECHNIQUES OF REGIONAL ANESTHESIA AND SEDO-ANALGESIA

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Postoperative cognitive dysfunction (POCD) is a common complication after cardiac and major non-cardiac surgery, at short and long terms, carrying a burden of suffering brought by decreased quality of life, increased morbidity, delayed functional recovery, and a prolonged hospital stay.

POCD is defined as a “deterioration of intellectual function presenting as impaired memory or concentration.” This condition is considered a mild neuro-cognitive disorder, and the diagnosis can only be made if the cognitive decline can be corroborated by the results of neuropsychological testing (presurgical and postsurgical). In addition testing must demonstrate that the individual has a new onset of cognitive deficits in at least two areas of cognitive functioning lasting two weeks after surgery or longer.

There is wide variation in the reported incidence of POCD in the literature. Much of this variation is due to methodological differences between the studies such as the use of varying test batteries, inadequate statistical power, the lack of adequate control subjects in the

studies and the lack of a standard criteria for diagnosing POCD. Rasmussen et al. demonstrated that the incidence of POCD in a group of 176 volunteers could vary between 0 percent and 40 percent if 10 different commonly used criteria for POCD were utilized.

Several studies had investigate and monitored the cognitive functions during and after various techniques of anesthesia, including functional neuroimaging such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), electrophysiological recordings like electroencephalogram (EEG), event-related potential (ERP) including the p300 component, bispectral index (BIS), and behavioural assessments by cognitive tests battery. However no data exist for the monitoring cognitive functions following integrated technique of peripheral nerve-block anesthesia and sedation-analgesia.

All findings suggest that there is no significant difference in the incidence of cognitive dysfunctions when a specific anesthetic or technique and type of surgery are compared. These datas emphasize that cognitive complaints after surgery may be caused by other factors such as depression or awareness of age-related changes, stress of the surgery, anxiety, postoperative pain. Outcomes from various studies differ, and no definite conclusion is possible.

The etiology of POCD is likely to be multifactorial but because the mechanisms are still ucertain it is difficult to identify prevention or treatment strategy. Elderly patients and orthopaedic surgery are specially susceptibles to this disorder which has implications for postoperative care of these patients. These observations are consistent whit the idea that advancing age and pain are a risk factor for POCD.

We compared the cognitive functions following two administration types of anesthesia: total intravenous anesthesia-target controlled infusion (TIVA-TCI) and integrated techniques of local regional anesthesia (LRA) and sedo-analgesia, under bispectral index guidance, in patients undergoing surgical procedure lasting ≥ 2 hours.

The patients cognitive status was assessed using a cognitive test battery including simplified MMSE, CFQ, WASR, DSST, OMCT, Hamilton scale for anxiety, undertaken preoperatively and at (6-12-24-48-36-72) hours postoperatively. We recorded the demand of postoperative analgesia using patient-controlled analgesia (PCA), visual analogue scale (VAS) for sedation and pain relief scores (PRS). POCD was defined as a Z score > 1.96 in two or more test parameters.

Preliminary results suggest that the incidence of POCD would be less with regional anesthesia rather than

general during the early postoperative period ,specially until 12 hours postoperatively.

In conclusion regional anaesthesia integrated with sedo-analgesia may decrease the incidence of POCD early after surgery, and only age , postoperative pain, surgical complications may be a risk factor for late postoperative cognitive dysfunction.

Bibliography:

1. Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. *Best Pract Res Clin Anaesthesiol* 2003;17:259–72.
2. Wu CL, Hsu W, Richman JM, Raja SN. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. *Reg Anesth Pain Med* 2004;29:257–68.
3. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc* 2000;48:618–24.
4. Ancelin ML, de Roquefeuil G, Ledesert B, et al. Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry* 2001;178:360–6.
5. Moller J, Cluitmans P, Rasmussen L, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 1998;351:857–61.
6. Canet J, Raeder J, Rasmussen LS, et al. Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand* 2003;47:1204–10.
7. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003;47:260–6.
8. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001;45:275–89.
9. Johnson T, Monk T, Rasmussen LS, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology* 2002;96:1351–7.
10. Rohan D, Buggy DJ, Crowley S, et al. Increased incidence of postoperative cognitive dysfunction 24 hr after minor surgery in the elderly. *Can J Anaesth* 2005;52:137–42.
11. Riis J, Lomholt B, Haxholdt O, et al. Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. *Acta Anaesthesiol Scand* 1983;27:44–9.

12. Williams-Russo P, Sharrock N, Mattis S, et al. Cognitive effects after epidural vs general anesthesia in older adults. *JAMA* 1995;274:44–50.
13. Urwin SC, Parker MJ, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. *Br J Anaesth* 2000;84:450–5.
14. Rogers MP, Liang MH, Daltroy LH, et al. Delirium after elective orthopedic surgery: risk factors and natural history. *Int J Psychiatry Med* 1989;19:109–21.
15. Lynch E, Lazor M, Gellis J, et al. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998;86:781–5.
16. Vaurio L, Sands L, Wang Y, et al. The role of pain and medications on postoperative delirium [abstract]. *Anesthesiology* 2004:A-39.
17. Duggleby W, Lander J. Cognitive status and postoperative pain: older adults. *J Pain Symptom Manage* 1994;9:19–27.
18. Herrick IA, Ganapathy S, Komar W, et al. Postoperative cognitive impairment in the elderly: choice of patient-controlled analgesia opioid. *Anaesthesia* 1996;51:356–60.
19. Rapp SE, Egan KJ, Ross BK, et al. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 1996;82:1043–8.
20. Silvasti M, Svartling N, Pitkanen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* 2000;17:448–55.
21. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003;58:76–81.
22. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;272:1518–22.
23. Adunsky A, Levy R, Heim M, et al. Meperidine analgesia and delirium in aged hip fracture patients. *Arch Gerontol Geriatr* 2002;35:253–9.
24. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
25. Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000;92:433–41.
26. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003;290:2455–63.
27. Kudoh A, Takase H, Takahira Y, Takazawa T. Postoperative confusion increases in elderly long-term benzodiazepine users. *Anesth Analg* 2004;99:1674–8.
28. Litaker D, Locala J, Franco K, et al. Preoperative risk factors for postoperative delirium. *Gen Hosp Psychiatry* 2001;23:84–9.
29. Leung J, Sands L, Mullen E, et al. Preoperative depression increases the risk of postoperative delirium in geriatric surgical patients. *Anesthesiology* 2004.
30. Zakriya KJ, Christmas C, Wenz JF Sr, et al. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. *Anesth Analg* 2002;94:1628–32.
31. Heyer EJ, Sharma R, Winfree CJ, et al. Severe pain confounds neuropsychological test performance. *J Clin Exp Neuropsychol* 2000;22:633–9.
32. P. F. White and H. Kehlet. Postoperative Pain Management and Patient Outcome: Time to Return to Work! *Anesth. Analg.*, March 1, 2007; 104(3): 487 – 489.
33. *Am J Geriatr Psychiatry* 15:50-59, January 2007. The Effects of Postoperative Pain and Its Management on Postoperative Cognitive Dysfunction Yun Wang, Ph.D., Laura P. Sands, Ph.D., Linnea Vaurio, B.A., E. Ann Mullen, B.S., and Jacqueline M. Leung, M.D., M.P.H.
34. Drug-induced Amnesia Is a Separate Phenomenon from Sedation: Electrophysiologic Evidence. *Anesthesiology*. 95(4):896-907, October 2001. Veselis, Robert; Reinsel, Ruth A. ; Feshchenko, Vladimir A.
35. Y. Wang, L. P. Sands, L. Vaurio, E. A. Mullen, and J. M. Leung. The Effects of Postoperative Pain and Its Management on Postoperative Cognitive Dysfunction. *Am J Geriatr Psychiatry*, January 1, 2007; 15(1): 50 – 59.
36. H. K. Fong, L. P. Sands, and J. M. Leung. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth. Analg.*, April 1, 2006; 102(4): 1255 – 1266.
37. Price CC, Garvan CW, Monk TG. Neurocognitive performance in older adults with postoperative cognitive dysfunction. *Anesthesiology*. 2003; 99:A50.
38. Bekker AY, Weeks EJ. Cognitive function after anaesthesia in the elderly. *Best Practice & Research Clinical Anaesthesiology*. 2003; 17:259-272.
39. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 60:1563-1568 (2005).

Are Preoperative Depressive Symptoms Associated With Postoperative Delirium in Geriatric Surgical Patients? Jacqueline M. Leung, Laura P. Sands - E. Ann Mullen, Yun Wang and Linne.

PATIENT CONTROLLED ANALGESIA

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During the last decade there has been a significant increase in the knowledge of basic cellular and molecular pain physiology. However the translation into improved clinical applications has been less substantial.

To improve postoperative recovery and surgical success, it is now well accepted to promote a multimodal protocol for perioperative analgesia which includes opioids, non-opioids, local anaesthetics and pain modulating substances like ketamine, gabapentin/pregabalin or corticosteroids, alongside early mobilisation and enteral feed. However, most perioperative analgesic protocols are still based on nurse administration of potent opioids. Given the fact that interindividual variations in analgesic requirements in the postoperative phase varies between 300-500%, it does not surprise that conventional application procedures are limited.

Patient-controlled analgesia systems using dedicated infusion devices have been shown in numerous studies to provide better pain control and greater patient satisfaction than conventional parenteral nurse-administered opioid analgesia. PCA demonstrated to overcome this high patient variability in analgesic demand. However, the Pk/Pd profile of the opioids used is usually not taken into account.

Although manual infusions of short acting opioids, like alfentanil and remifentanil, give acceptable stability once they equilibrated to a steady-state, it remains difficult to modify the blood concentration to different levels of analgesia in a controlled manner and infusion rates are likely to be chosen arbitrarily in clinical practice. In particular for remifentanil, studies in the immediate postoperative phase have shown a high incidence of side effects with manual infusions, yet with adequate analgesia.

The use of TCI technique in the postoperative phase of analgesia provides a rational approach for the continuation of the analgesic used intra-operatively. The first reported study of TCI for postoperative analgesia involved the administration of alfentanil to patients following major aortic surgery. Postoperatively, an alfentanil concentration was chosen for each patient to provide good analgesia with minimal respiratory

depression. Meanwhile, a couple of studies in patients undergoing different surgical procedures have proven the safety and efficacy of a patient-controlled administration of alfentanil using a demand button hand-set similar to that known from standard PCA devices. All studies have been reported to be associated with a high level of patient satisfaction. Recently, remifentanil has been studied as a patient-maintained TCI system to overcome the problems in analgesia known to be an issue in the immediate postoperative period after remifentanil based anaesthesia. The authors report a smooth transition to early postoperative analgesia after major orthopaedic surgery without respiratory side effects.

Standard PCA with opioids is commonly delivered via either the intravenous or epidural route. While patient satisfaction is usually considered high, the level of invasiveness, cost and involvement of nursing staff is definitely higher compared to more basic modes of administration. Several new PCA modalities are being developed to address these limitations. One of the most promising developments is a transdermal, credit-card sized PCA systems, which is based on iontophoretic fentanyl delivery (PCTS). This transdermal system delivers a preprogrammed amount of fentanyl, where the on-demand dosing and the pharmacokinetics of this system differ from the passive transdermal formulation of fentanyl used for chronic pain. Clinical studies have shown the efficacy in the management of acute postoperative pain and demonstrated safety and patient satisfaction.

Selected references:

1. J Clin Anesth 1993 ; 5 :182-93.
2. Cochrane Database Syst Rev 2006 ; 4 :CD003348.
3. Int J Clin Monit Comput 1992; 9:207-12.
4. Br J Anaesth 1997; 78:17-23.
5. Can J Anaesth 1996; 43:919-24.
6. Br J Anaesth 1998; 81:365-8.
7. Clin Pharmacokinetics 2005; 44 Suppl 1:1-6.

NEUROKININ-1 ANTAGONISTS

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Biological activities of neurokinins (NK) are mediated via NK receptors, which are divided into at least three types, NK1, NK2 and NK3, all of which are G-protein linked, with species homologues for each receptor type. SP is the preferred binding ligand for NK1 receptors,

NKA for NK2 receptors and NKB for NK3 receptors, although they do not act as exclusive agonists for the respective receptors. The NK1 receptor is upregulated at inflamed sites in a range of tissues that include joints (arthritis) and intestine (inflammatory bowel disease) and NK1 knockout mice have now been used in a range of studies relating to inflammation and pain showing reduced responses to certain inflammatory stimuli and to stimuli inducing moderate pain. A number of NK1 antagonists have been synthesised with improved selectivity and oral bioavailability. However, published results to date are disappointing and it is now generally accepted that NK1 antagonists do not have a beneficial effect in the treatment of human inflammatory pain conditions such as osteoarthritis. One possible reason for this failure is that, as these agents penetrate the CNS relatively poorly, they were not able to establish an adequate blockade of NK1 receptors at the doses used. The possibility that NK2 and NK3 receptor antagonists may also have therapeutic roles, especially in intestinal inflammation, has also been debated. Furthermore, dual NK1/NK2 antagonists have been proposed as treatments for inflammatory bowel disease and for asthma.

NK-1 receptor expressing cells appear to be critical in expression of spinal sensitization and of morphine-induced hypersensitivity. High opioid doses upregulate receptor expression in the dorsal horn and there is an increase in SP content and release. Blockade of the NK-1 receptor reversed morphine-induced hypersensitivity and mice lacking the NK-1 receptor did not develop morphine-induced hyperalgesia. In addition to blockade of opiate-induced hypersensitivity, ablation of NK-1 receptor expressing cells also inhibited opiate-induced changes indicative of central sensitization.

During the 1980s and 1990s, the neurogenic theory of migraine postulated that neurogenic oedema formation was an essential pathological feature in migraine. A number of nonpeptide receptor antagonists for the major vasoactive receptor for SP (the NK1 receptor) were shown to inhibit neurogenic oedema formation in the dura following trigeminal ganglion stimulation in the rat. Surprisingly, results from clinical studies for migraine have shown little beneficial effect of these agents. This may be because plasma protein extravasation may not occur in humans during migraine attacks. It is now suggested that the functional sensory nerves in the trigeminal system in humans include A-fibres that contain and release CGRP rather than SP and that this component of the trigemino-vascular system may be the more important factor in migraine.

The first registered clinical use for NK1 antagonists has been found in the treatment of emesis, associated with cancer therapies. The addition of an NK1 antagonist to standard antiemetic therapy improved the incidence of

emesis side effects in the acute, and especially in the delayed phase, by approximately 20%. Approximately 30-70% of high-risk patients experience postoperative nausea and vomiting (PONV) in the first 24 hours after surgery despite preoperative antiemetics such as intravenous 5HT3 receptor antagonists. NK1 receptor antagonists have demonstrable antiemetic activity against both peripheral and central emetic stimuli in both animal models and human clinical trials. Studies of Aprepitant (an NK1 antagonist approved for use as part of a combination regimen for prevention of chemotherapy induced nausea and vomiting) versus the 5HT3 receptor antagonist ondansetron for prevention of PONV in perioperative patients show that it is well tolerated. Although the treatments were similar for the primary endpoint of complete response (no vomiting and no use of rescue), aprepitant significantly improved protection against vomiting during the first 24 and 48 postoperative hours. Animal studies indicate that aprepitant occupies striatal NK1R by 100% for >48h despite brain levels being below the limit of detection after 24h. This slow functional reversibility appears to be associated with its long-lasting *in vivo* efficacy.

SP and NK1R are also expressed in brain regions that are involved in stress, fear and affective response and the SP content in these areas changes upon application of stressful stimuli. Also the central administration of SP produces a range of fear-related behaviours and the SP/NK1R system shows significant spatial overlap with neurotransmitters such as serotonin and noradrenaline, which are known to be involved in the regulation of stress, mood and anxiety. Therefore, it was hypothesised that blockade of the NK1R might have anxiolytic as well as antidepressant effects. Although an antidepressant effect of aprepitant has been demonstrated in clinical trials, the results are inconsistent and other neurokinins and/or neurokinin receptors might also be involved in the modulation of stress-related behaviour such that exclusive blockade of the NK1R might not be sufficient to produce reliable anxiolytic and antidepressant effects. Clinical trials to assess the antidepressant effects of NK2R antagonists are currently underway.

Thus, 75 years after their discovery, the tachykinins have been shown to possess biological activity in a wide variety of physiological and pathological systems, and the therapeutic potential of the tachykinin antagonists is still being evaluated.

References:

1. Lindstrom E et al. Neurokinin (NK)1 receptor antagonists: Correlation between *in vitro* receptor interaction and *in vivo* efficacy. *J Pharmacol Exp Ther.* 2007 Jun 15; [Epub]

2. Herpfer I, Lieb K. Substance P receptor antagonists in psychiatry: rationale for development and therapeutic potential. *CNS Drugs*. 2005;19(4):275-93.
3. Hill RG, Oliver KR. Neuropeptide and kinin antagonists. *Handb Exp Pharmacol*. 2007;(177):181-216.
4. King T et al. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. *Pain*. 2005 Aug;116(3):276-88.
5. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, Pueyo J, Chelly JE, Carides AD, Reiss T, Evans JK, Lawson FC. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind Phase III trial in patients undergoing open abdominal surgery. *Br J Anaesth*. 2007 Aug;99(2):202-11.

PK MODELS FOR PROPOFOL - SCHNIDER'S VIEW

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With the introduction of "Open TCI" into clinical practice a pharmacokinetic model for propofol other than the one used in the Diprifusor® became available for patient care. This new model included age as a covariate. This model published by Schnider et al. in 19981 was based on data from studies in patients of age 25 to 81. The model was also developed using state of the art population modelling techniques. During the studies the effect of propofol on the electroencephalogram (EEG) were also measured. With this information it was possible to develop a model for the effect site.²

Since the "Schnider – model" is available for TCI there is some debate about the "best model" for propofol. In this presentation we will highlight some of the properties of the Schnider model compared to the Diprifusor® model.

It is clinical common sense that the propofol dose must be adjusted so that is reduced in the elderly. This need for adjusting the dose is due to pharmacokinetic and pharmacodynamic reasons. In the elderly the concentrations are higher but the elderly patient is also more sensitive to the effects of propofol. By analysing the data from the elderly we found that the concentrations are particularly different between the older and younger subjects when the concentration is either increasing or decreasing. The Diprifusor(R) model does not include age as a covariate. Although the user has to enter age it is not used for the calculation of the

propofol input because in the population Gepts et. al.³ investigated the age range was narrow.

A major difference between the Diprifusor® model and the Schnider model is based on a full pharmacokinetic – pharmacodynamic study. The measured concentrations and the measured effect (EEG data) were modelled simultaneously. With this study design all the pharmacokinetic parameters which are necessary for prediction and control of the effect site concentration can be estimated. We found that the equilibration time constant (k_{e0}) was not affected by any of the considered covariates (such as age, height, weight and gender). Nevertheless it was observed that in the elderly it took longer until the maximal effect was reached. This is also predicted by the Schnider model.

Although it is possible to combine the parameters derived from a pharmacokinetic study with the results of a different study investigating the time course of the effect⁴ – this is suboptimal compared to a full pharmacokinetic – pharmacodynamic study.

It is noteworthy that the Diprifusor® (plasma control TCI) administers very similar amount of propofol over time compared to an effect site TCI using the Schnider model in a "average" subject. This is due to the much bigger and weight adjusted central volume (V_1) in the Diprifusor® model.⁵

The Schnider model has a fixed V_1 . Some people believe that the central volume is the main determinant of an induction dose. This assumption is wrong. In clinical practice we always target the effect site. With an induction dose we intentionally "overdose" the plasma because the gradient between the plasma and the effect site concentration is responsible for the drug moving between the two locations. After a bolus dose the concentration in the central compartment (blood) is very high. At this time the concentration in the effect site on the other hand is very low. The plasma concentration is decreasing rapidly because propofol is distributed into peripheral compartments. The concentration at peak effect⁴ is therefore dependent on the initial concentration in the plasma, which is determined by the volume of the central compartment but at least as much by these distribution processes. Because age affects the size of the fast initial distribution, the size of the bolus in TCI effect site control with the Schnider model depends on age.

In conclusion the Schnider model includes the important covariate age and is a model which can be used for effect site TCI. Users of the model are encouraged to use the Schnider model only in effect site TCI.

References:

1. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of

method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; 88: 1170-1182

2. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; 90: 1502-16

3. Gepts E, Camu F, Cockshott ID, Douglas EJ: Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia* 1987; 66: 1256-1263

4. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; 99: 324-33

5. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. 1991; 67: 41-48

DRUG INTERACTIONS IN ANAESTHESIA

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Drug interactions in anaesthesia may be of pharmaceutical, pharmacokinetic or pharmacodynamic origin. This lecture concerns those interactions that are the result of pharmacokinetic and/or pharmacodynamic alterations.

Pharmacokinetic Interactions in Anaesthesia.

Interindividual pharmacokinetic variability is in the order of 70%. As a result different patients receiving similar anaesthetic dosing regimens may vary in blood and effect site concentrations by up to 70%. Two important determinants of pharmacokinetic variability are pharmacogenetics and pharmacokinetic interactions. Genetic variability probably is predominantly responsible for the huge interindividual variability in hepatic enzyme activity. For example alfentanil metabolism is catalysed predominantly, if not exclusively, by cytochrome P450 3A3/4. Interindividual variability in human alfentanil disposition and alfentanil drug interactions may be attributable to individual differences in P450 3A3/4 activity. Furthermore, the P450 enzyme system is subject to inhibition and induction by concomitant administration of different agents. Well known P450 enzyme inducers are the antiepileptic agents phenytoin and phenobarbitone and the antibiotic rifampicine that increase oral contraceptive and opioid metabolism and thus affect the effectiveness of these agents. Erythromycin and the calcium channel blocker diltiazem are important inhibitors of the P450

enzymes and have been described to diminish the metabolism of midazolam and alfentanil resulting in prolonged hypnosis especially after oral midazolam administration.

The first suggestions of pharmacokinetic interactions between propofol and the various opioids go back to 1993. Schüttler et al. then revealed on the basis of a NONMEM population pharmacokinetic analysis that fentanyl and alfentanil both increased the volume of the central compartment and the clearance of propofol. More recently, Pavlin et al. showed that in the presence of alfentanil at plasma concentrations of 40 ng/ml, with patients still breathing spontaneously, blood propofol concentrations were increased by 20%. Furthermore, Matot et al. showed that the first-pass pulmonary uptake of propofol in cats was reduced from 60% to 40% after pre-treatment with fentanyl. A reduced first-pass pulmonary uptake of propofol may increase the initial blood propofol concentration after a bolus dose administration. Vice versa both Gepts et al. and Pavlin et al. reported on the increased plasma alfentanil concentrations in the presence of propofol. This may be the result of the, thus far only in vitro described, inhibition of the oxidative metabolism of alfentanil by the cytochrome P450 enzyme after administration of propofol. Also sufentanil metabolism appears to be inhibited in the presence of propofol. Other sedative agents that interfere with the metabolism of opioids are midazolam and dexmedetomidine that have been shown to inhibit the metabolism of alfentanil, and pregnenolone that has been shown to induce alfentanil metabolism in vitro. Recently, two pure pharmacokinetic interaction studies shed more light on this subject. In the presence of a constant blood propofol concentrations of 1.5 µg/ml alfentanil pharmacokinetics were significantly changed. Propofol increased the mean plasma alfentanil concentrations by approximately 15%. Propofol decreased the C₁₁ of alfentanil by 15%, C₁₂ by 68%, C₁₃ by 51%, and lag-time by 62%. Mean arterial pressure and systemic vascular resistance were significantly lower in the presence of propofol suggesting that the haemodynamic changes induced by propofol may be the cause of the pharmacokinetic interaction. This pharmacokinetic interaction was furthermore expressed by the longer context-sensitive half-time of alfentanil during combined infusion with propofol. Propofol increases the context-sensitive half-time of alfentanil by 3 min on average for durations of infusions ranging from 6 to 240 min. Similarly, in the presence of alfentanil propofol concentrations increase as well. Alfentanil reduces the clearance of propofol and increases the deep distribution volume (V₃). Next to alfentanil also heart rate proved a significant covariate in the mixed effects analysis of the pharmacokinetics of propofol in this study. Tachycardia reduces blood propofol concentrations by an increased hepatic perfusion

whereas in the presence of bradycardia blood propofol concentrations tend to be elevated.

In conclusion, it becomes increasingly evident that propofol and the opioids affect each other's distribution and elimination. Further studies are necessary to evaluate the precise mechanisms that cause these pharmacokinetic interactions.

Pharmacodynamic Interactions in Anaesthesia:

Numerous examples of synergistic drug interactions exist in anesthesiology, including interactions between two drugs (e.g., propofol and midazolam) or of a single drug delivered to two sites (e.g., spinal and supraspinal morphine). Such synergistic interactions imply distinct sites of action, such as different anatomical sites, cell populations, or signaling pathways/receptor sites within the same cells. Conversely, additive interactions imply convergent actions on the same protein site, molecular pathway, or cellular site.

Over the past decade a fast amount of studies on pharmacodynamic anaesthetic drug interactions has occurred. On the basis of these data one may now conclude for various clinical end points whether we may benefit from the interaction between the various groups of anaesthetic agents. Is it possible to increase the speed of induction on the basis of propofol-opioid interactions? Opioids have been shown to decrease propofol requirements for induction of anaesthesia. It is therefore possible to improve speed of induction using propofol-opioid combinations, simply because in the presence of high opioid concentrations lower effect site propofol concentrations are needed for loss of consciousness and these are more rapidly reached. Because the time to peak effect differs for propofol and the various opioids, the timing of the opioid bolus administration relative to that of propofol is critical in this respect. Times to peak effect for propofol, remifentanyl, alfentanil, fentanyl and sufentanyl are 2 min, 1.2 min, 2 min, 4 min and 7.5 min. To benefit most of the hypnotic requirement reducing power, the opioid sufentanyl thus should be given way in advance of propofol compared to remifentanyl or alfentanil.

Is it possible to increase the haemodynamic stability of the induction of anaesthesia on the basis of propofol-opioid interactions? Opioids reduce the hypnotic dose requirements for induction of anaesthesia. In theory, this may lead to an improved haemodynamic profile of the induction of anaesthesia. However, in ASA 1-2 patients this dose reduction does not lead to a more stable induction of anaesthesia. In elderly patients or patients suffering from cardiovascular instability high opioid-low propofol anaesthesia may be associated with increased haemodynamic stability during induction of

anaesthesia, however, no data are available regarding this yet.

Is it possible to decrease the time to return of consciousness postoperatively on the basis of propofol-opioid interactions? Opioids reduce intraoperative propofol requirements and affect propofol concentrations at which patients regain consciousness. In the presence of still significant concentrations of alfentanil e.g. propofol concentrations have to decrease much further for patients to awaken postoperatively compared to those patients that have no significant alfentanil levels. From these data optimal propofol-opioid concentrations have been determined that assure adequate anaesthesia and the most rapid possible return of consciousness after termination of the infusions. In general propofol-remifentanyl anaesthesia is associated with the most rapid return of consciousness after any infusion duration compared to fentanyl, sufentanyl or alfentanil. Another benefit of remifentanyl is that even at suboptimal high remifentanyl concentrations return of consciousness is not postponed significantly.

What are the optimal propofol-opioid concentrations for anaesthesia in patients allowing spontaneous respiration? So far, no clinically relevant data regarding propofol-opioid interactions for spontaneous respiration have been described. Bouillon et al. described for a single agent alfentanil the clinical profile in this respect. The EC₅₀ for adequate ventilation during normocapnia with alfentanil is 60 ng/ml. With higher plasma alfentanil concentrations the arterial PCO₂ first has to increase significantly to maintain adequate ventilation. Similarly, for propofol it has been shown that with increasing concentrations both the response to hypercapnia and to hypoxia is diminished. This means that in the presence of propofol hypoxia will be deeper and hypercapnia more severe before a ventilatory response will be evoked by these stimulants. Because no interaction data exists, nor data regarding the effect of clinically meaningful nociception on propofol-opioid respiratory depression, optimal propofol-opioid concentrations that assure adequate anaesthesia and adequate respiration cannot yet be defined.

Conclusion: In everyday clinical practice anaesthesiologists are confronted with a huge variability in the dose-response relationship of the agents they administer to their patients. Pharmacokinetic and pharmacodynamic interactions are, in part, responsible for this variability. To some extent, a thorough knowledge and application of interaction data from the literature into clinical practice allows for a more stable anaesthetic and may improve patient safety.

References:

Luurila H, Olkkola KT, Neuvonen PJ: Interaction between erythromycin and the benzodiazepines

diazepam and flunitrazepam. *Pharmacol.Toxicol.* 1996; 78: 117-22

Olkkola KT, Ahonen J, Neuvonen PJ: The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth.Analg.* 1996; 82: 511-6

Backman JT, Olkkola KT, Neuvonen PJ: Rifampin drastically reduces plasma concentrations and effects of oral midazolam. *Clin.Pharmacol.Ther.* 1996; 59: 7-13

Ahonen J, Olkkola KT, Neuvonen PJ: Effect of itraconazole and terbinafine on the pharmacokinetics and pharmacodynamics of midazolam in healthy volunteers. *Br.J.Clin.Pharmacol.* 1995; 40: 270-2

Kharasch ED, Thummel KE: Human alfentanil metabolism by cytochrome P450 3A3/4. An explanation for the interindividual variability in alfentanil clearance? *Anesth.Analg.* 1993; 76: 1033-9

Pavlin DJ, Coda B, Shen DD, Tschanz J, Nguyen Q, Schaffer R, Donaldson G, Jacobson RC, Chapman CR: Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. *Anesthesiology* 1996; 84: 23-37

Janicki PK, James MF, Erskine WA: Propofol inhibits enzymatic degradation of alfentanil and sufentanil by isolated liver microsomes in vitro. *Br.J.Anaesth.* 1992; 68: 311-2

Chen TL, Ueng TH, Chen SH, Lee PH, Fan SZ, Liu CC: Human cytochrome P450 mono-oxygenase system is suppressed by propofol. *Br.J.Anaesth.* 1995; 74: 558-62

Kharasch ED, Hill HF, Eddy AC: Influence of dexmedetomidine and clonidine on human liver microsomal alfentanil metabolism. *Anesthesiology* 1991; 75: 520-4

Mertens MJ, Vuyk J, Olofsen E, Bovill JG, Burm AGL: Propofol alters the pharmacokinetics of alfentanil in healthy male volunteers. *Anesthesiology* 2001; 94: 949-57

Mertens, M. J., Vuyk, J., Burm, A. G. L., Olofsen, E., and Bovill, J. G. The pharmacokinetic interaction between propofol and alfentanil in healthy male volunteers. *Br.J.Anaesth.* (V80), A424

Bovill JG: Analysis of drug interactions, *Drug Interactions*. Edited by Bovill JG. Bailliere Tindall, 1998, pp 153-68

Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL: Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; 92: 1603-16

Berenbaum MC: What is synergy? *Pharmacol.Rev.* 1989; 41: 93-141

Berenbaum MC: Concepts for describing the interaction of two agents. *Radiat.Res.* 1991; 126: 264-8

Vuyk J: The effect of opioids on the pharmacokinetics and pharmacodynamics of propofol, On the study and practice of intravenous anaesthesia. Edited by Vuyk J, Engbers F, Groen-Mulder S. London, Kluwer Academic Publishers, 2000, pp 99-111

Kazama T, Ikeda K, Morita K: Reduction by fentanyl of the Cp50 values of propofol and hemodynamic responses to various noxious stimuli. *Anesthesiology* 1997; 87: 213-27

Mertens MJ, Vuyk J, Parivar K, Engbers FH, Burm AG, Bovill JG: Pharmacodynamic interaction of eltanolone and alfentanil during lower abdominal surgery in female patients. *Br.J.Anaesth.* 1999; 83: 250-2

Vuyk J, Engbers FH, Burm AGL, Vletter AA, Griever GE, Olofsen E, Bovill JG: Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia. *Anesthesiology* 1996; 84: 288-99

Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. *Anesthesiology* 1994; 81: 820-8

Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. *Anesthesiology* 1995; 83: 8-22

Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG: Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology* 1997; 87: 1549-62

Bouillon T, Schmidt C, Garstka G, Heimbach D, Stafforst D, Schwilden H, Hoeft A: Pharmacokinetic-pharmacodynamic modeling of the respiratory depressant effect of alfentanil. *Anesthesiology* 1999; 91: 144-55

SEDATION

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Sedation involves pharmacological depression of the central nervous system whilst maintaining the response to verbal commands and preserving protective airway reflexes. Awareness of the surroundings is decreased and physiological and psychological stress can be ameliorated. It is often important for patients to be cooperative during the procedure and to avoid unnecessary involuntary movements. Successful sedation will make the surgeon's task easier, improve patient satisfaction and confidence for any subsequent visits. Medications for conscious sedation should ideally have the following properties:

1. Titratability (rapid onset and offset)
2. No pain on injection
3. No adverse effects
4. Wide margin of safety (wide therapeutic index)
5. Relatively easy to administer and use

To date, no one agent fulfils all these criteria. Commonly used medications for conscious sedation can have adverse effects such as hypotension, respiratory depression, persistent drowsiness and amnesia, dizziness, unsteadiness of gait, paradoxical reactions and dreaming. Some of these reactions can make the surgical procedure more difficult and adversely affect the patients. Doctors administering the sedative medications should have the knowledge and skills to deal with these problems. A number of drugs are available for sedation and analgesia and their safe use depends on a thorough knowledge of pharmacology, appropriate use (e.g. sedative drugs are not suitable for patients in pain), early recognition and ability to deal with side effects. Benzodiazepines have been popular in the past, although propofol is gaining in popularity. Opioids are not good sedatives but have synergistic effects with such drugs. However the use of combinations of opioid and sedative drugs can lead to respiratory depression, obstruction or cardiovascular compromise. Dexmedetomidine produces sedation via its effects on the locus coeruleus with EEG activity similar to natural sleep and, consequently, facilitated arousal with less propensity for confusional states. It is also analgesic and does not depress respiration, although airway obstruction can still occur. Many authorities have attempted to promulgate guidelines on the conduct of sedation and patient monitoring in an attempt to reduce the high rate of complications especially in the hands of non anaesthesiologists.

References:

1. Dexmedetomidine: handbook of clinical applications. Irwin MG, Wong GTC. Lippincott Williams & Wilkins ISBN 0781771358. 2006.

2. A double blind crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee HY. *Anaesthesia and Analgesia*. In press.
3. A comparison of dexmedetomidine and midazolam for sedation during wisdom teeth extraction. Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng JKF, Irwin MG. *Anaesthesia*. In press.
4. Rohrich, R. J. *Plast. Reconstr. Surg.* 114: 201, 2004.
5. ASA. Guidelines for Office-Based Anesthesia. 2004.

OPIOID PHARMACOGENETICS

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Polymorphism derives from a single base mutation in DNA that substitutes one nucleotide for another. This is called a single nucleotide polymorphism or an SNP. The pivotal importance of SNPs was recognized soon after their discovery, and it has become a key objective to map all of these variants across the entire human genome. The effect of any particular SNP i.e. the resulting phenotype, will, however, depend on the impact of the resulting substitution of the encrypted amino acid on the respective protein. This effect will vary depending on both amino acid substituted and its position.

In pain management it is apparent that patients' respond differently to opioid therapy and current evidence suggests that this is related to genetic variability. Genetic factors regulate opioid pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) and contribute to such variability. Single-nucleotide polymorphisms in the mu opioid receptor gene are associated with increasing morphine, but not methadone dosage requirements and altered efficacy of mu opioid agonists and antagonists. Genetic variability in non-opioid systems may also indirectly influence clinical opioid efficacy e.g. genetic inactivity of cytochrome P450 (CYP) 2D6 occurs in about 8% of the Caucasian population (only 1-2% of Chinese) and renders codeine ineffective (lack of morphine formation), decreases the efficacy of tramadol (lack of formation of the active O-desmethyl-tramadol) and slightly decreases the clearance of methadone. Another 5% have multiple copies of the CYP2D6 gene and are ultrarapid metabolisers. Opioid bioavailability can be altered by the function of membrane transporters e.g. P-glycoprotein, thereby affecting CNS distribution and elimination and even drug uptake into metabolising organs/cells. Polymorphisms in enzyme systems also

affect the formation of active metabolites e.g. M-6-G, or opioid clearance. Variability in an enzyme-degrading catecholamine (COMT) gene may alter the efficacy of morphine. ABCB1 genotypes also inconsistently influence opioid pharmacodynamics and dosage requirements.

Receptor binding and a wide range of pharmacological studies have proposed several μ receptor subtypes, but only one μ opioid receptor (Oprm) gene has been isolated. These variants all show the same selectivity for μ opioids but major differences in binding affinity, potency and efficacy among these variants as well as in their anatomical localization. These variants may provide insights into the wide range of opioid responses among these agents observed clinically and opens new avenues in designing selective drugs based upon their efficacy and potency rather simple binding affinity.

Pharmacogenetics may be able to individualize pharmacotherapy and improve care by predicting the optimal dose and avoiding side effects and toxicity in individual patients.

References:

1. Genetic Predictors of the Clinical Response to Opioid Analgesics. Clinical Utility and Future Perspectives. Lotsch J, Skarke C, Liefhold J, Geisslinger G. Clin Pharmacokinet 2004; 43 (14): 983-1013.
2. Genetics and variability in opioid response. Stamer UM, Bayerer B, Stuber F. Eur J Pain. 2005; 9(2):101-4.
3. Sweeney PB. Pharmacogenomics and anaesthesia: explaining the variability in response to opiates. European Journal of Anaesthesiology 2007, 24: 209-212.
4. Somogyi AA et al. Pharmacogenetics of Opioids. Clinical Pharmacology & Therapeutics 2007; 81, 429-444.

TCI AND PHARMACOGENOMICS

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Standard TCI algorithms may incorporate predictors of inter-individual variability including age, weight and race. These factors incorporate both environmental and genetic variables that influence an individual's response to a drug. Genetic polymorphisms are more specific differences between individuals that in concert with environmental factors may influence the concentration of drug achieved with a given dose (pharmacokinetics), as well as the patient's response to a given effect site concentration (pharmacodynamics). It has been

predicted that at least 20% of variability in drug responses is due to genetic differences. As a result, understanding genetic polymorphism a potentially powerful approach to inter-individual variability. A genetic polymorphism is defined as a nucleotide difference present in more than 1% of the population. Over 1.4 million single nucleotide polymorphisms have been identified in the human genome including about 600,000 in the gene coding regions.

One day in the future, patients may have their genotype for certain pharmacologically important targets determined at the time of preoperative testing along with their EKG, blood counts and chemistry. Knowledge of genotype and associated risks may obviate the need for some preoperative screening. However, currently the study of genetic polymorphism and drug behavior is mostly in the research domain. We will discuss the potential for polymorphism in metabolic enzymes to describe variability in pharmacokinetic relationships. The liver enzyme CYP3A4 is important for the dealkylation of fentanyl and sufentanil. In one study of Chinese volunteers they identified 20 different polymorphisms in this enzyme with a population frequency between 1-37%. It would not be surprising if some of these polymorphisms had functional effects on enzyme efficacy and were predictive of fentanyl and sufentanil concentration.

Differences in a single nucleotide can also predict differences in drug effect. A polymorphism in the opioid receptor gene OPRM1 alters the binding and activity of b-endorphin at the m-opioid receptor (2). Furthermore, polymorphisms in OPRM1 are predictive of baseline pain sensitivity. The response to steady state morphine-6-glucuronide concentrations are also affected by OPRM1 genotype (3). OPRM1 genotype affects the use of morphine via PCA as well (4). One would expect that if OPRM genotype were known, it could be used as a covariant to predict inter-individual variability in the pharmacodynamic response to all opioids. If such a variable were included in a data set derived from a large population, a patient with unknown genotype could be potentially phenotyped with data from a closed-loop system. This information could be important in the setting of multiple required anesthetics such as in burn care.

Potential studies of today will provide the "state of the art" tomorrow. With sequencing of the human genome and the increased availability and reduced cost of patient genotyping, these powerful tools to address inter patient variability are available now for our use.

(1) Liu et al. (2005) Future Medicine 6, 731-747

(2) Bond et al. (1998) Proc. Natl. Acad. Sci. 95, 9608-9613

(3) V. M. Steen et al. (1997) Mol. Psychiatry 2, 139

(4) Chou et al. (2006) *Anesthesiology* 105, 334–7

MECHANISMS OF DRUG ACTION

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John Langley (1878), while studying the actions of atropine and pilocarpine on salivary flow in cats, wrote that “there is some substance or substances in the nerve ending or gland cell with which both atropine and pilocarpine are capable of forming compounds”. In a later publication, he referred to this as a “receptive substance”.

Paul Ehrlich (1913), while working with the treatment of infectious diseases using drugs derived from the German dye industry, wrote that a drug could have a therapeutic effect only if it has the “right sort of affinity” and that the “combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed receptor”. At this time Ehrlich visualised receptors as being part of side-chains in mammalian cells, whereas today we realise that drug-binding sites may be part of any cellular constituent.

In 1926, A. J. Clark and J. H. Gaddam almost simultaneously published key papers on the actions of acetylcholine and atropine on the frog's isolated heart and the actions of adrenaline and ergotamine on the rabbit uterus. They were the first to introduce the log concentration-effect curve. Clark followed A. V. Hill in relating the hyperbolic shape of the dose-response curve for acetyl choline to the drug-receptor binding equation.

This presentation will discuss briefly occupation theory, rate theory, and allosteric theory. Occupation theory can be used in some cases to derive information about receptor-drug interactions from measurements of response. Rate theory seemed to be able to explain some important aspects of receptor-effect coupling, but was not supported by any data. Allosteric theories are the most complete descriptions of receptor-effect coupling, but the existence of microscopic constants that are difficult to measure experimentally make these models difficult to apply.

In the foreseeable future we might be able to depict, at high resolution, exactly what happens when a ligand binds to its receptor and explain why this leads on to, for example, channel opening or G-protein binding. Most importantly, hopefully we will be able to design ligands de novo to modulate specific receptors.

A more complete handout is available at URL:

<http://pkpdtools.com/downloads/pdf/mechanisms.pdf>

HUMAN ERROR, RISK ASSESSMENT AND REDUCTION OF INFUSION PUMPS

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It has been nearly seven years since release of the Institute of Medicine (IOM) report entitled “To Err is Human”, and the establishment of patient safety and quality improvement as a top priority around the world. There is growing recognition that human error risks and hazards of health care associated injury and harm are a result of poor system reliability due to systemic design problems rather than poor performance by individual providers.

Donnabedian developed the structure - process - outcome model which has served as a conceptual framework for health services research for over 30 years. In the case of patient safety, there is concern that risks and hazards that are hard wired within the structure, process and technology of care have the potential for causing injury and/or harm to patients. Organizational pathogens--latent conditions within both the process and structure of care – can set up the sharp-end health care providers for failure. Thus, to achieve the outcome of safe care, both the structure, processes and technology of care must be modified before these latent conditions become active and cause unintended and avoidable patient harm. Accurate identification of the root causes of events must precede identification and implementation of appropriate interventions. Moreover, solutions for risk associated with human behavior or active failures such as skill-based failures are different than the embedded hazards or latent failures in organizational process and structure. The use of sophisticated risk assessment techniques including process mapping, failure modes effects analysis (FMEA), and probabilistic risk assessment (PRA) can be used to identify at which point interventions are most appropriate.

The presentation will review effective learning and risk assessment tools that can be used to assess and manage the risk associated with infusion pumps. In order for organizations and individuals to become safe, they must make sense of their engineered environment and learn from harmful events. The ultimate goal of sensemaking is to build the understanding that can inform and direct actions to eliminate risk and hazards that are a threat to patient safety. Sensemaking serves as a conceptual framework to bring together well established approaches to assessment of risk and hazards: 1) at the single event level using process maps and root cause analysis (RCA), 2) at the processes level using (FMEA) and 3) at the system level using (PRA). The results of these separate

or combined approaches are most effective when end users in conversation-based meetings add their expertise and knowledge to the data produced by the RCA, FMEA and/or PRA in order to make sense of the risks and hazards. Without ownership engendered by such conversations, the possibility of effective action to eliminate or minimize infusion pump harm will be greatly reduced.

The audience will gain an understanding of potential solutions and techniques used to analyze infusion pump adverse and near miss clinical events, as well as the barriers surrounding the safe use of TIVA infusion pumps.

PUMP SAFETY

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Intravenous drug delivery in Europe is usually by means of a syringe pump. In the early days of IV drug applications these pumps were merely a replacement for the inaccurate drip infusions that ran by gravity. Only basic alarm functions were available and in some pumps the syringe was not even fixed so that free flow of drug into the patient when the pump was placed above the patient (siphoning) was possible. Although many anecdotal stories of mishaps with infusion pumps can be heard in technical departments in hospitals, very little has been published in the past on the clinical consequences of technical or user caused failures of these devices. Although infusion devices are extremely important instruments for the anaesthesiologist to get the right amount of drug into the patient, until recently they usually did not receive the same technical care and attention as for example a vaporizer or a ventilator. An overwhelming number of recent publications however show that medication errors may have an important influence on patient outcome and hospital costs¹. This has drawn attention to the infusion pump both as a source^{6,8} of possible error and as an instrument^{4,9} in the chain of measures for prevention of medication errors. Possible failing in delivering the right amount of drug to the right patient on the right time with a syringe infusion pump can have many sources.

Inability to deliver the right dose:

- Equipment failure

Although infusion pumps are well engineered, all systems can fail. For this reason scheduled and documented checks by authorised personal are required (and mandatory in some countries). This seems a trivial remark but the nature of the infusion pump and the way it often travels between departments and even between

hospitals can make this check an organisational challenge.

- Inappropriate user handling

Not being aware of specific properties of the devices can be a major source of problems:

- Siphoning

This may happen when a syringe is placed high above the patient. Dependent on the type of syringe the phenomena can already occur on a height of 80 cm. The usual scenario is that the syringe is placed in the pump for future use without fixing the plunger in the pump holder. When the patient then is prepared for transport the syringe pump maybe placed on a piece of monitor equipment. A 50 ml syringe will empty this way within 5-7 minutes. Another less likely source of siphoning is when a syringe is correctly placed in the syringe pump but there is somewhere a leak allowing air to enter the syringe. At present there are anti siphoning valves available that increase the resistance in the infusion line so that no hydrostatic under-pressure will occur in the syringe. Disadvantage of these valves is that they do not contribute to a more regular pump flow².

- Delayed startup^{5,7}

Compliance of the syringe an infusion lines together with air in the system may cause a delay in delivery at start-up of the device. Dependent on the flow rate, syringe size, slack in syringe fitting this delay can vary from minutes to more than half an hour. Delay in occlusion alarm is mainly dependent on the same factors and is heavily influenced by the amount of air in system¹¹.

- Dead space¹¹

When outputs of more syringe pumps are connected by stopcocks and extension lines a complicated flow and drug concentration pattern will exist at the final entrance point in the patients. Changing the rate of one pump will temporarily change the concentration and infusion rates of the drugs from the other infusion pumps and hence cause an unpredictably change the resulting drug effects. Although every clinician has seen this phenomena (often called flush but in fact it is more complicated) in practice when using for example vaso-active drugs, very little is known on how this may affect the patient.

- Pump level³

Recent research have shown that even changing the height of the infusion pump may change the flow coming from it. This may work two ways: changing the position of the patient may also influence temporarily the flow of the syringe pump. Compliance of the complete infusion system, air in the syringe slack of syringe fitting, infusion rate and syringe size play a role.

Inability to enter the right dose (for the right patient):

Complicated devices at the present time surround clinicians. These devices have different user interfaces and ergonomical designs. Often functions are available that are not required in the current situation and may confuse the user. Sometimes other functions like for example timed bolus is so difficult to find that the user selects a less optimal method of administration. There is lack of standardization in units of dosing, drug dilutions and even the way of displaying and labelling the drug and its concentrations between hospitals, departments and even within a department. This is an obvious source of error. Training, retraining and maybe even certification maybe required in the future

New generation of 'smart' pumps tries to help avoiding these sources of errors by introducing drug libraries in pumps with soft and hard limits that can be made drug, hospital, department or even type of patient dependent⁹. Implementation and maintenance of these pumps is not simple and requires cooperation between pharmacists, clinicians, technicians and ICT departments and the pump and software manufactures^{4,9}. Techniques for syringe/drug recognition with barcodes or chips, cheap and reliable technology that can be found in every warehouse, is desperately needed.

Inability to determine the right dose:

Intelligence implemented in pumps for (anesthetic) drug delivery nowadays even go a step further. With Target Controlled Infusion(TCI) it is possible to dose an intravenous drug not in mass/kg but on the base of a calculated concentration. To discuss the advantages of TCI goes beyond the scope of this abstract but like every new technology it has its own scope of errors. How for example to deal with a failing TCI device or what happens if patient data are not reset between two surgical procedures¹⁰. An even more disquieting observation is that quite often these systems are controlled by not well-trained personal ("Yes I understand how it works, but how do I deliver a bolus?"). Another disturbing factor is the availability of different models for the same drug. Concerning the implementation of pharmacokinetic models in TCI no appropriate guidelines and requirements exist for manufacturers that want to develop and market such a system. This has led to the regrettable situation that at least for propofol TCI is dependant on the model selected, which is undoubtedly a source for confusion and error despite the advanced technology.

1. David M. Benjamin. Reducing Medication Errors and Increasing Patient Safety J. Clin. Pharmacol. 2003; 43; 768

2. C. McCarroll, D. McAtamney, R. Taylor. Alteration in Flow delivery with antisiphon devices. Anaesthesia, 2000, 55, pages 355-357

3. H.Kern et all. Downward movement of syringe pumps reduces syringe output. Br.J .Anaesth 2001;86 828-831

4. M Husch et all. Insights from the sharp end of intravenous medication errors: implications for infusion pump technology .Qual. Saf. Health Care 2005;14;80-86

5. T. Neff et all Start-up delays of infusion syringe pumps Paediatric Anaesthesia 2001 11: 561±565

6. Deborah B Reengineering Intravenous Drug and Fluid Administration. Processes in the Operating Room Anesthesiology 2002; 97:139-47

7. Neff, SB. Flow rate, syringe size and architecture are critical to start-up performance of syringe pumps. Eur J Anaesthesiol 2007; 24(7):602-8

8. D. Heise.et al. Sources of faults and dangers in the use of syringe drivers: accidental occlusion of the infusion system. Anaesthesist 1998 · 47:54-58

9. Jeffrey M. Rothschild et all.A controlled trial of smart infusion pumps to improve medication safety in critically ill patients Crit Care Med 2005 33, 3, 533-540

10.Engbers F, Practical use of 'Diprifusor' systems. Anaesthesia 1998, 53, Supplement 1:28-34

11.Engbers F. Total intravenous anaesthesia:the equipment. In:On the study and practice of Intravenous anaesthesia. Kluwer Academic Publishers, ISBN: 9780792360797

SAFETY REQUIREMENTS OF TIVA: PK DRUGS, CORRECT DRUG & CONCENTRATION

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Although intravenous anesthesia has many advantages it is technically more demanding than anesthesia with volatile anaesthetics. This is true for computer controlled drug administration, but also for traditional constant rate infusions with syringe pumps. The setting is very different since the drugs have to be prepared for every patient and the drug administration pathway of volatile anaesthetics through the airway is tightly monitored because of other reasons! Some of the safety requirements apply to intravenous anesthesia in general some specifically to target controlled infusion (TCI).

Bacterial contamination of drugs is a major concern. In the early 1990s an outbreak of sepsis in intensive care units based on contamination of propofol prompted the manufacturer to take immediate action. This led to a change in the formulation of propofol that is, since then a bactericidal agent is added to it. A recent survey showed that despite guidelines many anaesthesiologists

are re-using the syringes of i.v. drug between patients.1 Whether reusing a syringe after exchanging parts of the tubing system (anti-reflux valve etc.) is safe remains unproven.

It goes without saying that for i.v. anaesthesia proper i.v. access is a pre-requisite. Furthermore it is best to have access to venous puncture site during anaesthesia because it can happen that the tip of a venous catheter penetrates the venous wall during the anaesthetic with resulting paravenous infusion. The tubing system also deserves special attention. Dead space has to be minimal. In addition every anaesthesiologist should be aware of the size of the dead space, because depending on the concentration of the drug significant amount of drug can be "stored" in it. Prefabricated tubing systems for total i.v. anaesthesia (TIVA) are available. They also include the necessary anti-reflux valves. Nowadays, anti-reflux valves are mandatory for i.v. anaesthesia, without which dangerous backflow of drug is possible. There are many cases known where backflow lead to patient awareness during surgery. Because drug flow can be interrupted at different levels (syringe pump, backflow, disconnection, para-venous infusion etc.) in the paralysed patient it is mandatory to use a depth of hypnosis monitor in many institutions. It must be noted that these monitors do not prevent awareness per se but help to detect the technical problem.2

When using a rational mode of drug administration, that is TCI, the anaesthesiologist has to choose a pharmacokinetic model. With open TCI it is important that the pharmacokinetic model which is used for control matches the drug in the syringe. For drugs which have to be prepared before use (e.g. remifentanyl) the final concentration in the syringe deserves special attention. Depending on the combination of the concentration of propofol (1% or 2%) and remifentanyl (e.g. 100 mic/ml or 50 mic/ml) gross overdosing of the drugs can be prevented in case the pharmacokinetic model is mixed up. Prefilled syringes are an option for prevention of drug mix-up. The first implementation of TCI for clinical use the Diprifusor[®] used such a system with automatic detection of the drug in the syringe. With a systematic setup process of the syringe pumps and a propofol concentration of 1% and remifentanyl 50 mic/ml dangerous events can be minimized with open TCI at much lower cost.

TIVA and TCI require more attention to details. There are some pitfalls which can be avoided by setting in place clear safety standards for i.v. anaesthesia.

References:

1. Halkes MJ, Snow D: Re-use of equipment between patients receiving total intravenous anaesthesia: a postal survey of current practice. *Anaesthesia* 2003; 58: 582-7

2. Luginbuhl M, Schnider TW: Detection of awareness with the bispectral index: two case reports. *Anesthesiology* 2002; 96: 241-3

TCI ANAESTHESIA: MANUAL, SEMI-AUTOMATED OR CLOSED LOOP CONTROL?

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Fatigue is an associated factor in 6% of the critical incidents resulting from human error in anaesthesia and reduced vigilance is shown in deprived sleep conditions (1). Automated general anaesthesia might help to decrease these related risks. Closed loop anaesthesia systems have been developed linking one controlled variable with the automated titration of one anaesthetic drug.

The ideal properties of a control anaesthetic variable are that it will be measured continuously and instantaneously. Moreover, any change in underlying state must cause a change in the variable. The control variable should have a limited variability during steady state conditions and a lack of hysteresis. Ideally it should be widely used and validated as well as independent of patient characteristics (age, sex) and of the selected anaesthetic drug.

The development of electroencephalographic indices of anaesthetic depth has in turn generated interest in automated anaesthesia delivery systems using these as the input variable. Several studies have related the BIS index to the closed loop administration of propofol by TCI (2, 3). The first studies were performed in ASA I, II patients in small groups of patients using different analgesic techniques with or without the use of a muscle relaxant. All these studies demonstrate an adequate control of the depth of anaesthesia, no awareness, good haemodynamic stability and a short awakening time but they were limited to the maintenance period of general anaesthesia.

Puri et al have compared their own black box closed loop TCI propofol titrated to the BIS with a manual control of propofol delivery in 40 ASA I-II patients undergoing elective surgery. Closed loop anaesthetic delivery led to lower induction doses of propofol and less overshoot of the target BIS. The closed loop system maintained BIS to within +/-10 of target for a significantly longer time during the maintenance phase of anaesthesia and smaller amounts of anaesthetic agent were required. There was also faster postoperative recovery using the automated delivery of propofol.

Liu et al have compared their closed-loop versus a manual control titration of Propofol TCI for anaesthetic induction and maintenance guided by the BIS in a

prospective randomized multicenter study (5). A broader range of surgery was explored and elderly patients were included. 160 patients were recruited. Induction was faster in the Manual TCI group (N= 80) than in the closed-loop group (N =80) but BIS overshoot (less than 40) was more pronounced. During maintenance the change of propofol Target per hour was 11 times in the manual group and 33 times in the closed loop group. BIS was maintained in the 40-60 interval during $70 \pm 21\%$ of the anaesthesia time in the manual group and $89 \pm 9\%$ of the time in the closed loop group. The extubation time was significantly reduced in the closed loop control group (10 ± 7 minutes versus 7 ± 4 minutes). The number of patients with a longer extubation time than 10 minutes was also significant (N = 28 (35 %)) in the manual group versus (N = 12 (15%)) in the closed group. No patient reported intraoperative recall. The authors concluded that closed loop titration of effect site propofol TCI was better than manual titration to maintain BIS within the 40-60 range with a similar haemodynamic stability.

These interesting results are challenging and several questions are still unsolved.

1) Is there a best EEG monitoring?

Bonhomme et al have studied the correlation and agreement between BIS and state entropy (SE) of the EEG during propofol anaesthesia at different clinical endpoints (6). BIS and SE were globally well correlated but agreement was poor as differences of more than 20 units were frequently observed except for awake and paralysed patients. In another study protocol, BIS and SE differed by more than 20% in only 6 cases over 140 measurements. The range of SE was smaller than BIS and SE showed a better correlation with propofol Ce than BIS (7). So, the BIS or the Entropy monitoring seems to be equivalent and both could be recommended as an input variable in an automated propofol TCI delivery system.

2) Is 50 the appropriate target for any EEG parameter whatever the anaesthesia technique and what is the influence of the anaesthesia technique on the EEG target figure?

Using frontal, central and parietal electrode montages, the corresponding BIS values were simultaneously recorded with a BIS A1000 monitor during 10 minutes at the propofol concentration (Gepts set) allowing LMA insertion in 20 ASA I-II, 18-62 yr, non obese patients (8). At the same predicted effect propofol target concentrations, the mean BIS values were 32, 46 and 58 for the frontal, central and parietal leads, respectively. A change of the calculated BIS value has also been described depending if the frontal EEG is recorded at the left or right side.

Lysakowski et al also demonstrate an effect of fentanyl, alfentanil, remifentanyl and sufentanil TCI on LOC and BIS value during propofol induction of anaesthesia (9).

The effects of a bolus of ketamine 0.5 mg kg⁻¹ on BIS, RE and SE during surgery under sevoflurane anaesthesia was associated with a significant increase in BIS, RE and SE (10). This increase is considered as paradoxical in that it is associated with a deepening level of hypnosis. Muscle relaxation may also confound interpretation of entropy monitoring (11).

In a prospective study incorporating 1064 adult patients undergoing major noncardiac surgery under general anaesthesia, BIS was blinded to the anaesthetist. Among the comorbidity factors, intraoperative hypotension and cumulative deep hypnotic time (time where BIS < 45) were 2 significant independent predictors of 1 yr mortality (12). A too low BIS target in unhealthy patients could be questioned!

On the contrary, Farag et al investigate whether depth of anaesthesia as determined by BIS affects postoperative neurocognitive function after 4 to 6 weeks in patients older than 50 yr. Patients were anaesthetised with a standard isoflurane technique and were randomized to either higher BIS target values between 50 and 60 or to lower BIS values between 30 and 40 (13). The patients of the lower BIS levels during majority of procedures performed better on psychological tests as late as 4-6 wk postoperatively. The authors concluded that the depth of anaesthesia may affect cognitive performance or that isoflurane has neuroprotective effects by decreasing the cerebral metabolic rate.

So, BIS values can change according to the location of the EEG recording. The delay to get the figure, the influence of the placement of the probe, the risk of artefacts such as the electrocauterisation or a pace maker and the paradoxical changes of ketamine can confound the anaesthetist to select the appropriate EEG target value for his patient. The Anaesthetist must know the limits of the proposed EEG value by the different EEG algorithms. Moreover we must question if the EEG target has to be the same for each patient whereas some patients loose consciousness at more than 60 and other one at 40!

3) Can we close the loop of TCI anaesthesia using other input parameters?

Auditory evoked potentials were more able to detect the transition from unconsciousness to consciousness (14). Auditory evoked potentials also showed better correlation with the propofol effect site concentration (15). Auditory evoked potentials measure different aspects of neural processing during anaesthesia. This gives rise to the hypothesis of Schwilden et al that simultaneous monitoring of the EEG, AEP and SSEP

may give additional information compared with the monitoring of each quantity alone (16).

4) Which sensor to monitor analgesia?

In contrast to hypnosis, there is no ideal surrogate parameter for analgesia in anesthetized patients. Some authors have proposed to measure the pupil diameter dilation. Other authors have tried to use the heart rate variability as a marker of the autonomic nervous system responsiveness. In the daily clinical practice, the anaesthetist still titrates the analgesic component to suppress blood pressure and heart rate responses to noxious stimulation.

In 13 patients undergoing spine surgery, Luginbühl et al have developed a closed-loop of mean arterial blood pressure during surgery with alfentanil TCI infusion which allows adequate peroperative alfentanil dosage. After induction with propofol, alfentanil, and mivacurium and tracheal intubation, isoflurane was titrated to maintain the BIS at 55 (+/- 5), and the alfentanil administration was switched from manual to closed-loop control. The authors' controller has a similar set-point precision as previous hypnotic controllers and provides adequate alfentanil dosing during surgery. This may be a further step toward a multiple input-multiple output controller.

We have compared the manual control of remifentanyl propofol TCI anaesthesia technique with a semi-automated propofol-remifentanyl effect-site TCI Anaesthesia using the BIS and the systolic arterial pressure as the input variables. In the semi automatic group, the number of propofol and remifentanyl TCI adaptations was higher and the level of the target concentrations was lower than in the manual group. Moreover, the percentage of BIS within the predefined range was significantly greater.

Today, there is a need of good and multiple sensors to monitor not only the hypnotic component but also the analgesic component. Clinicians are not convinced that general anaesthesia can be simplified for all the types of patient, surgery and moreover for the different phases of general anaesthesia (induction, maintenance and emergence) using only one input linked to one anaesthetic drug output using even a very complex algorithm. Future computer assisted IV anaesthesia systems have to be developed by using several input parameters related to the administration of the simultaneous delivery of the hypnotic and analgesic drugs. Does the anaesthetist be confident to a unique black box closed loop system to use in any patient or situation is questionable. A computer system allowing the anaesthetist to control the limits of the input and output parameters according to the selected anaesthesia technique and the intensity of the nociceptive stimulation seems a more logical approach.

The future development of multiple input-output systems will probably help the anaesthetist by giving more time even during critical events and by allowing reducing the instances of under or excessive dosing. It may reduce the risk of human errors due to the fatigue.

Adequate clinical judgement, physiological response analysis and selected monitoring tools remain the standard of care to optimize Anaesthesia in 2007. My personal opinion is that the most important will always remain the pilot and not the sensor or the algorithm!

References:

- 1) Murray D, Dodds C. The effect of sleep disruption on performance of anaesthetists--a pilot study. *Anaesthesia* 2003; 58 (6):520-5.
- 2) Mortier E, Struys M, De Smet T, Versichelen L, Rolly G. Closed-loop controlled administration of propofol using bispectral analysis. *Anaesthesia*. 1998 Aug;53(8):749-54.
- 3) Absalom AR, Sutcliffe N, Kenny GN. Closed-loop control of anaesthesia using Bispectral index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anaesthesia. *Anesthesiology*. 2002 Jan;96(1):67-73.
- 4) Puri GD, Kumar B, Aveek J. Closed-loop anaesthesia delivery system (CLADS) using bispectral index: a performance assessment study. *Anaesth Intensive Care*. 2007 Jun;35(3):357-62.
- 5) Liu N, Chazot T, Genty A, Landais A, Restoux A, McGee K, Laloe PA, Trillat B, Barvais L, Fischler M. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study. *Anesthesiology*. 2006 Apr;104(4):686-95.
- 6) Bonhomme V. et al, *B J Anaesth* 2006; 97:340-6. Correlation and agreement between Bispectral Index and state entropy of the EEG during Propofol Anaesthesia.
- 7) Iannuzzi M, Iannuzzi E, Rossi F, Berrino L, Chiefari M. Relationship between bispectral index, electroencephalographic state entropy and effect-site EC50 for propofol at different clinical endpoints. *Br J Anaesth*. 2005 May;94(5):613-6.
- 8) Pandin P, Van Cutsem N, Tuna T, D'hollander A. Bispectral index is a topographically dependent variable in patients receiving propofol anaesthesia. *Br J Anaesth*. 2006 Nov;97(5):676-80.
- 9) Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanyl and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. *Br J Anaesth*. 2001 Apr;86(4):523-7.

- 10) Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. *Br J Anaesth.* 2005 Mar;94(3):336-40.
- 11) Hans P, Giwer J, Brichant JF, Dewandre PY, Bonhomme V. Effect of an intubation dose of rocuronium on Spectral Entropy and Bispectral Index responses to laryngoscopy during propofol anaesthesia. *Br J Anaesth.* 2006 Dec;97(6):842-7.
- 12) Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg.* 2005 Jan;100(1):4-10.
- 13) Farag E, Chelune GJ, Schubert A, Mascha EJ. Is depth of anesthesia, as assessed by the Bispectral Index, related to postoperative cognitive dysfunction and recovery? *Anesth Analg.* 2006 Sep;103(3):633-40.
- 14) Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anaesthesia during propofol anaesthesia. *Br J Anaesth.* 1999 May;82(5):672-8.
- 15) Vereecke HE, Vasquez PM, Jensen EW, Thas O, Vandebroecke R, Mortier EP, Struys MM. New composite index based on midlatency auditory evoked potential and electroencephalographic parameters to optimize correlation with propofol effect site concentration: comparison with bispectral index and solitary used fast extracting auditory evoked potential index. *Anesthesiology.* 2005 Sep;103(3):500-7.
- 16) Schwilden H, Kochs E, Daunderer M, Jeleazcov Ch, Scheller B, Schneider G, Schuttler J, Schwender D, Stockmanns G, Poppel E. Concurrent recording of AEP, SSEP and EEG parameters during anaesthesia: a factor analysis. *Br J Anaesth.* 2005 Aug;95(2):197-206.
- 17) Luginbuhl M, Bieniok C, Leibundgut D, Wymann R, Gentilini A, Schnider TW. Closed-loop control of mean arterial blood pressure during surgery with alfentanil: clinical evaluation of a novel model-based predictive controller. *Anesthesiology.* 2006 Sep;105(3):462-70.

PERIOPERATIVE PAIN MANAGEMENT

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The control of postoperative pain is a major challenge for the anesthesiologists. Indeed, it has been shown that efficient postoperative pain control is not only necessary for the patient's well-being - patient satisfaction (1,2) -

but it also has a positive impact on the outcome of surgery, as recently shown by Capdevila et al. (2), who demonstrated that the choice of analgesia technique may influence early rehabilitation after major knee surgery. Moreover, Sentürk et al. (3) were able to show that a good postoperative pain control after thoracotomy decreases the prevalence of chronic pain assessed six months after surgery. In this study, the authors postulated that there is a relation between the intensity of postoperative pain and the appearance of chronic pain.

Among the intravenous pain drugs, opioids - morphine - remain one of the mainstays. Opioids exert their analgesic effect by interacting with the μ receptor. However, opioid analgesic action is limited by their almost exclusive blockade of C fibers and some pain modulation within the central nervous system. The weak blocking action on the A delta fibers explain the lack of efficacy of opioid during movement - mobilization - rehabilitation. Moreover, a growing body of evidence suggest that opioid analgesics can elicit delayed hyperalgesia (exaggerated nociceptive response to noxious stimulation) in experimental models after repeated opioid administration (4) or continuous delivering (5). It has also been shown that a single administration of opioid also induces a long-lasting increase of basal pain sensitivity, leading to delayed hyperalgesia (6). There is now a substantial amount of evidence that glutamate via N-methyl-D-aspartate (NMDA) receptor play a pivotal role in the development and maintenance of central hyperactive states underlying the behavioral manifestations of pain facilitation, such as hyperalgesia, allodynia and spontaneous pain (7). It was shown that ketamine pretreatment in rats can prevent long-lasting hyperalgesia induced by acute administration of fentanyl (8). Usefulness of ketamine has been limited by its undesirable psychic emergence effects and cardiovascular stimulating properties. However, it is becoming increasingly clear that a distinction must be made between the use of high-dose ketamine for anesthesia and the use of low-dose ketamine for analgesic and anti-hyperalgesic effects. A recent review article (9), which included randomized, prospective, controlled, double-blind studies, and reported pain scores was able to demonstrate that continuous pain scores, was able to demonstrate that continuous infusion of 0.3-0.5 mg.kg-1.h-1 improves postoperative pain management and reduces opioid related adverse effects. The application of the enantiomer S(+)-ketamine deserves further studies, since this isomer is 3-4 times more potent than R(-)-ketamine for pain relief and at equianalgesia doses produces fewer psychic disturbances and less agitation than R(-)-ketamine or the racemate (10,11).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are part of the armamentarium of the multimodal management of postoperative pain and may have a significant

opioid-sparing effect after major surgery, since they are able to counteract the actions of the inflammatory mediators released by the surgical trauma. Their use was, however, limited by the non-availability of intravenous preparation and the high incidence of gastrointestinal side-effects. It was shown that surgical trauma results in induction of cyclooxygenase-2 (Cox-2), leading to the release of prostaglandins, which sensitize peripheral nociceptors and produce localized hyperalgesia (primary hyperalgesia) (12). The inhibition of Cox-1 results in upper gastrointestinal bleeding and hematological side-effects (13,14). Therefore, selective Cox-2 may be of great interest in the management of postsurgical pain, particularly with the new injectable formulation (15), which are preferred in acutely painful conditions. Concerns dealing with thromboregulation (Cox-2) (16,17) and inhibition on bone formation (18) secondary to Cox inhibitors have been raised and further studies are needed to clarify these issues.

References:

1. Borgeat A, Schäppi B, Biasca N, Gerber C. Patient-controlled analgesia after major shoulder surgery. *Anesthesiology* 1997;87:1343-1347
2. Borgeat A, Tewes E, Biasca N, Gerber C. Patient-controlled interscalene analgesia with ropivacaine after major shoulder surgery PCIA vs PCA. *Br J Anaesth* 1998;81:603-605
3. Sentürk M, Özcan PE, Talu GK, Kiyani E, Camci E, Özyalcin S, Dilege S, Pembeci K. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002;94:11-15
4. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain* 1995;62:259-274
5. Kissin I, Bright CA, Bradley EL Jr. Acute tolerance to continuously infused alfentanil: the role of cholecystokinin and N-methyl-D-aspartate-nitric oxide systems. *Anesth Analg* 2000;91:110-116
6. Laulin JP, Célèrier E, Larcher A, Le Moal M, Simonnet G. Opiate tolerance to daily heroin administration: an apparent phenomenon associated with enhanced pain sensitivity. *Neuroscience* 1999;89:631-636
7. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993;52:259-285
8. Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiol* 2000;92:465-72

9. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. *Pain* 1999;82:111-125

10. Marietta MP, Way WL, Castagnoli Jr N, Trevor AJ. On the pharmacology of the ketamine enantiomers in the rat. *J Pharmacol Exp Ther* 1977;202:157-165

11. Calvey TN. Isomerism and anaesthetic drugs. *Acta Anaesthesiol Scand* 1995;106:83-90

12. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ. Interleukin-1 β -mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 2001;410:471-475

13. Simon LS. Are the biologic and clinical effects of the Cox-2-specific inhibitors an advance compared with the effects of traditional NSAIDs? *Curr Opin Rheumatol* 2000;12:163-170

14. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch RW, Eisen G, Agrawal NM, Stenson WF, Butt AM, Zhao WW, Kent JD, Lefkowitz JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib long-term arthritis safety study. *JAMA* 2000;284:1247-1255

15. Barton SF, Langeland FF, Snabes MC, LeComte D, Kuss ME, Dhadda SS, Hubbard RC. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology* 2002;97:306-314

16. Marcus AJ, Broekman MJ, Pinsky DJ. COX inhibitors and thromboregulation. Clinical implications of basic research. *N Engl J Med* 2002;347:1025-1026

17. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-1528

18. Aspenberg P. Avoid cox inhibitors after skeletal surgery. *Acta Orthop Scand* 2002;73:489-490

GLUCOCORTICOIDS FOR POSTOPERATIVE PAIN CONTROL

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The corticosteroids are natural hormones or synthetic analogues which act on receptors in the cell nucleus. They have to diffuse into the cell-nucleus initiating changes in the transcription of DNA to proteins and then subsequently the clinical effects are seen. This is a time-consuming process for slow effect onset, but the changes in cellular protein expression will obviously go on for some time after the drug is cleared from plasma, with the result of prolonged effects. There are probably also some direct membrane and/or receptor effects of glucocorticoids as well, because analgesic effect may be demonstrated already after one hour and some other effects even more rapidly.

As corticosteroids are inhibitors of both phospholipase and cyclo-oxygenase type II, important in the synthesis of prostaglandins, they have analgesic effect. Paracetamol, NSAIDs and corticosteroids have a ceiling of analgesic effect, not being sufficient as mono-therapy after more extensive surgery. However, there seems to be an additive effect of all these three classes of drugs, suitable for a multimodal, opioid sparing regimen; effective even after major surgery. It seems like the glucocorticoid dose for post-operative analgesia must be somewhat higher than the antiemetic dose, at least 8 – 16 mg of dexamethasone (or equivalent dose of other corticosteroids) is needed for analgesic effect, typically peaking at 3-4 hrs. It seems that the duration of analgesic effect is long after a single dose of IV glucocorticoids. In the study of Hval et al the effect was significant until 3 days after administration. In a study of Romundstad, a single dose of 125 mg methylprednisolone was analgesic for 3 days, whereas Bisgaard et al report reduced pain through 1 week after a single dose of dexamethasone 8 mg during laparoscopy. The plasma elimination half-life of dexamethasone is only about 6 hrs, thus there seems to be ongoing drug effects for a significant period after drug clearance from the plasma. Recently there is also a report from Romundstad et al. on pre-emptive use of glucocorticoids, having impact on the incidence of chronic pain. In a study of females due for breast augmentation, pre-operatively receiving either 125 mg methylprednisolone, 40 mg parecoxib or placebo; there was a significant reduction in the incidence of pain in the wound area at 1 year after surgery; 30% of the patients in the methylprednisolone group; 53% in the two other groups.

The corticosteroids also have other effects which may be useful in the post-operative setting: anti-emetic, anti-fever, stimulation of appetite, anti-drowsiness and anti-allergic. Typically they do not have some of the side-effects of the NSAIDs, such as renal failure, cardiovascular incidents or allergic reactions.

However, the side-effects of corticosteroids are known and feared after long-term use: infections, gastric

ulceration, reduced wound healing and hormonal changes in general. After single use or short-term use (i.e. up to some days) virtually no side serious effects have been reported, apart from rare cases of psychiatric disturbance. However, the patients may be reported to be a little more alert and euphoric after glucocorticoid medication, some having less sleep during the first post-operative night.

Litterature:

Holte K. J Am Coll Surg 2002;195:694-712

Henzi I. Anesth Analg 2000;90:186-194

Aasboe V. Anesth Analg 1998;87:310-23

Halvorsen P. Anesth Analg 2003;96:1578-83

Romundstad L. Anesth Analg 2006;102:418-25

Hval K. Anesth Analg 2007: in press (august number)

Romundstad L. Pain 2006;124:92-9

Buchman AL. J Clin Gastroenterol 2001;33:289-94

PHARMACOKINETICS AND PHARMACODYNAMICS OF PARACETAMOL

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Since paracetamol (N-acetyl-p-aminophenol, acetaminophen, APAP) is insoluble in water, the water soluble propacetamol (N,N-diethylester of paracetamol) form has been available for more than 15 years. Following IV bolus infusion, plasma esterases rapidly hydrolyse the prodrug of paracetamol. Solubilisation, along with special buffer systems and the addition of antioxidants led to the development of a new, ready to use IV paracetamol solution. Paracetamol has long been thought as having a similar mechanism as aspirin because of the similarity in structure. It has been assumed that paracetamol acts by reducing the production of prostaglandins, present in processes such as pain and fever, by inhibiting the cyclooxygenase (COX) enzyme. However, there are important differences between the effects of aspirin and those of paracetamol. Prostaglandins participate in the inflammatory response which is why it has been known to trigger symptoms in asthmatics, but paracetamol has no appreciable anti-inflammatory action and hence, does not have this side effect. Furthermore COX also produces thromboxanes which aid in blood clotting, aspirin reduces blood clotting, but paracetamol does not. Finally, aspirin and the other NSAID'S commonly have detrimental effects on gastric mucosa where prostaglandins serve a protective role, but paracetamol is

safe. Indeed, while aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's activity site, paracetamol indirectly blocks COX, and this blockade is ineffective in the presence of peroxides. This might explain why paracetamol is effective in the CNS and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. In 2002 it was reported that paracetamol selectively blocks a variant of the COX enzyme that was different from the then known variants, COX1 and COX2. This enzyme, which is only expressed in the brain and in the spinal cord, is now referred to as COX3. Its' exact mechanism of action is still poorly understood, but future research may provide further insight. A single study has shown that administration of paracetamol increases the bioavailability serotonin (5-HT) in rats , but the mechanism is unknown to date in humans.

Metabolism:

Paracetamol is metabolised primarily in the liver, where most of it (60-90% of a therapeutic dose) is converted to inactive compounds by conjugation with sulphate and glucuronide, and then excreted by the kidneys. Only a small portion (5-10% of a therapeutic dose) is metabolised via the hepatic cytochrome P450 enzyme system (specifically CYP2E1); the toxic effects of paracetamol are due to a minor alkylating metabolite (N-acetyl-p-benzo-quinone imine abbreviated as NAPQI) that is produced through this enzyme, not paracetamol itself or any of the major metabolites. The metabolism of paracetamol is an excellent example of toxication, because the metabolite NAPQI is primarily responsible for toxicity rather than paracetamol itself. This is especially true in the situation of massive doses where the metabolite NAPQI dangerously increases. In normal situations the metabolite is rapidly detoxified by the reduced glutathione and is eliminated by the kidneys following conjugation with cysteine and mercaptouric acid. Paracetamol metabolites are excreted principally by the kidneys. Ninety percent of the administered dose is excreted within 24 hours, in the glucuronide form (60-80%) and sulphate conjugated (20-30%) while less than 5% is eliminated unmodified.

NSAID's and Paracetamol: Paracetamol, unlike other common analgesics such as aspirin, has very little anti-inflammatory properties, and is thus not a member of the class of drugs known as non steroidal anti-inflammatory drugs. In recommended doses, paracetamol does not irritate the GI tract, affect PTT or renal function as much as NSAID's. Paracetamol is safe during pregnancy, and does not affect the closure of foetal ductus arteriosus as NSAID's can. Unlike aspirin, it is safe in children since paracetamol is not associated with the risk of Reye's syndrome in children. Like NSAID's and unlike opioids, paracetamol has not been found to cause euphoria or alter mood in any way. Paracetamol and NSAIDs have

the benefit of bearing a low risk of addiction, dependence, tolerance and withdrawal, but, unlike opioid medication may easily damage the liver if the narrow therapeutic range is exceeded, but this is generally taken into account when compared to the danger of paracetamol., particularly in combination with weak opioids.

Toxicity: In humans, paracetamol has a narrow therapeutic index, the therapeutic dose is close to the toxic dose, in spite of this, paracetamol is contained in many preparations. In other animals, such as cats, even small doses are toxic. This means that despite being one of the most widely used analgesics available at recommended doses, there is a large potential for overdose and toxicity. Without timely treatment, paracetamol overdose can lead to liver failure and death within days. Because of the wide over the counter availability of this drug it is sometimes used in suicide attempts by those unaware of the prolonged timecourse and high morbidity and mortality associated with paracetamol induced toxicity. The toxicity dose of paracetamol is highly variable. In adults, single doses above 10 g or 150mg/kg have a reasonable likelihood of causing toxicity. Toxicity can also occur when multiple smaller doses within 24 hours exceeds these levels, or even with chronic ingestion of doses as low as 4g daily, and death with as little as 6g/day. In children acute doses above 200mg/kg could potentially cause toxicity. There are some risk factors for toxicity such as chronic excessive ethanol consumption that can induce CYP2E1, thus increasing the potential toxicity of paracetamol. Fasting is a risk factor, possibly because of depletion of hepatic glutathione reserves. It is well documented that concomitant use of the CYP2E1 inducer isoniazid increases the risk of hepatotoxicity. Concomitant use of other drugs which induce CYP enzymes such as antiepileptics (including carbamazepine, phenytoin, barbiturates etc) have also been reported as risk factors.

Pharmacokinetics: Pharmacokinetics of paracetamol after IV administration was best described by a 2 compartment model with a clearance of 18 l/h/70 kg, intercompartmental clearance of 45.7 l/h/70 kg, central volume of distribution of 13.2 l/ 70 kg and peripheral volume of distribution of 33.0 l/ 70 kg. Paracetamol levels in plasma decline multiphasically with a mean clearance after IV administration of 352 + - 40 ml/min. A 2 compartment open model appeared to describe the decline adequately. The pharmacokinetics and pharmacodynamics of propacetamol in neonates of different gestational age is different from that of adults. Serum half life was 277 min in preterm infants and 172 min in term infants. Clearance was 0.116 l/kg/h in the preterm infants and 0.170 l/kg/h in term infants. A correlation was found between gestational age and the serum half life of propacetamol. Post infusion bioavailability of paracetamol (500mg and 1g) is similar

to that observed following infusion of propacetamol. Pharmacokinetics of paracetamol is linear up to 2g, as a single shot and after repeated doses within 24h. The maximum plasmatic concentration (Cmax) of paracetamol observed at the conclusion of IV infusion of 500mg and 1g in 15 mins was respectively around 15ug / ml and 30ug/ml. Volume distribution of paracetamol is approx. 1 l/ kg. Paracetamol does not bind well to plasmatic proteins. After an infusion of 1g of paracetamol significant concentrations were observed (approx. 1.5ug/ ml) in the cefalo- rachidian liquid following 20min infusion. Pharmacokinetics of paracetamol does not alter in the elderly.

References:

1. Brodie BB, Axelrod J. (1948). "The Fate of Acetanilide in Man" J Pharmacol. Exp Ther 94 (1): 29-38
2. Boutaud O, Aronoff DM, Richardson JH, Marnett LJ, Oates JA (2002) . " Determinants of the Cellular Specificity of Acetaminophen as an Inhibitor of Prostaglandin H2 Synthesis. Proc. Natl. Acad Sci USA 99 (10) 7130-5
3. Swierkosz TA, Jordan L, McBride M, McGough K, Devlin J, Botting RM (2002) . " Actions of Paracetamol on Cyclooxygenases in Tissue and Cell Homogenates of mouse and rabbits. Med Sci Monit 8 (12) : BR496-503
4. Pina LA, Sandrini M, Vitale G (July 11, 1996). " The antinociceptive action of paracetamol is associated with changes in the serotonergic system in the rat brain ". Eur J Pharmacol 308 (1) : 31-40
5. Cola' S, Chacartegui R, Temprano Gonzalez R, Gamez Aruza C, Muatoz Cacho P, Pascual Gamez J (2005). "Abuse pattern of Analgesics in Chronic daily headache: a Study in the general population". Rev Clin Esp 205 (12) : 583-7
6. Sheen C, Dillon J, Bateman D, Simpson K, MacDonald T (2002). "Paracetamol toxicity: Epidemiology, prevention and cost to the Health Care system." QJM 95 (9) : 609-19
7. Wurthwein G, Kolling S, Reich A, Hempel G, Schultz- Westhoff P, Pinheiro VP, Boos J (2005) "Pharmacokinetics of Intravenous Paracetamol in children and adolescents under major surgery". Eur J Clin Pharmacol 60: 883-888
8. Rawlins MD, Henderson DB, Hijab AR (1977). "Pharmacokinetics of Paracetamol (Acetaminophen) after Intravenous and Oral administration". Eur J Clin Pharmacol 11: 283-286
9. EN, Karlsson MO (1999). "Xpose-an S-PLUS based population pharmacokinetic/pharmacodynamic model

building aid for NONMEM". Comput Methods Programs Biomed 58: 51-64

10. Allegaert K, Van der Marel CD, Debeer A, Pluim MAL, Van Lingen RA, Vanhole C, Tibboel D, Devlieger H (2004). "Pharmacokinetics of Single dose Intravenous Propacetamol in Neonates: Effect of Gestational age". Arch Dis Child Fetal Neonatal , 89: F25-F28

PERIOPERATIVE OPTIMIZATION

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Introduction: Optimization perioperative care means to personalize anesthesia to patient needs. In fact age, associate pathology (heart, lung, kidney failure), cognitive problems can influence intra and postoperative periods and finally a good outcome. Every stage of our work hides the danger of adverse effects, due to drugs and procedures. The best choice should be to utilize synergistic effect of different techniques but to minimize negative effects.

Premedication: Opioids offers a good protection for anxiety, a light sedation during ALR procedures and decrease intraoperative opioids amount during general anesthesia but take care in the patients with lung and heart diseases and in children because of their adverse effects. Benzodiazepines are useful for decrease anxiety and for light sedation during surgery by regional anesthesia. Take care in elderly patients for paradoxical effect (dissociation). During deep sedation or anesthesia by TCI infusion benzodiazepines may cause mistake in device accuracy. Pharmacologic premedication can be replaced with exhaustive talk with the patient.

ALR Techniques: A wide choice of central and peripheral blocks provides optimal anesthesia for unilateral and bilateral surgery (orthopaedic, urology, gynaecology, abdominal and thoracic). Continuous techniques also provides a very good quality postoperative analgesia. Peripheral blocks for upper limb are interscalenic, infraclavicular and axillary approach to brachial plexus and indications are respectively shoulder, arm and hand surgery. Peripheral blocks for lower limb are lumbar and femoral blocks for anterior part and sciatic nerve block (proximal and caudal) for posterior part of lower limb. Lumbar, femoral and sciatic (parasacral, subgluteal, lateral approach) are very useful for to place catheter for analgesia in major orthopaedic interventions. Peripheral nerve blocks are the first choice respect to central blocks in orthopaedic because of

better haemodynamic stability and no interferences with antithrombotic therapy. However, low dose and concentration spinal and epidural anesthesia also provides haemodynamic stability. Uncomfortable position and stress can require different level of sedoanalgesia or light general anesthesia.

Sedoanalgesia: Sedoanalgesia techniques are complementary to ALR procedures because guaranteed comfort and sedation for stressful surgical procedures. Painful position due to patient osteoarthritis, psychological problems, surgeon manoeuvre may be eliminated to optimize sedation. Main drugs are propofol, midazolam and remifentanyl administered by infusion devices (TCI) and adequate neurological monitoring (BIS or AEP). If sedoanalgesia is deep and the patient is unconscious airway control is advisable (by LMA). Sedoanalgesia decrease pain threshold but is not substitute of a nerve block failure. Moreover, effective drug dosage is variable patient to patient therefore titration is advisable. Another recommendation is to avoid additive haemodynamic effects between spinal or epidural local anesthetics and propofol.

Postoperative Pain Control: Continuous peripheral and central nerve blocks guaranteed better postoperative analgesia than PCA *e.v.* infusion of systemic analgesics (opioids and NSAIDs). Nevertheless an administration of systemic analgesics can decrease incident pain, another side pain and allow to obtain a global analgesia (multimodal analgesia). We prefer paracetamol rather than NSAIDs because their negative effect on blood coagulation. Local anesthetics (LA) by PCRA mode are suitable for continuous peripheral nerve blocks for upper and lower limbs and continuous epidural blocks for lower abdominal surgery. LA and/or opioids are suitable for epidural administration for high abdominal and thoracic surgery. While adverse effects of peripheral blocks are local as infection or nerve injury (rare) epidural blocks have systemic effects as hypotension and local as epidural haematoma (rare) and infection.

References:

1. Singelyn FJ, Deyaert M, Joris D, Et Al. Effects of Intravenous Patient-Controlled Analgesia with Morphine, Continuous Epidural Analgesia, and Continuous Three-In-One Block On Rehabilitation After Unilateral Total Knee Arthroplasty. *Anesth Analg* 1998; 87: 88–92.
2. Chelly JE, Greger J, Gebhard R, Et Al. Continuous Femoral Blocks Improve Recovery and Outcome of Patients Undergoing Total Knee Arthroplasty. *J Arthroplasty* 16; 2001: 436–45.
3. Horlocker TT, Wedel DJ. Anticoagulation and Neuraxial Block: Historical Perspective, Anesthetic

Implications, and Risk Management. *Reg Anesth Pain Med* 1998; 23: 129–34.

4. Chelly JE. Complications. IN: Chelly JE, Casati A, Fanelli G, Eds. *Continuous Peripheral Nerve Block Techniques*. Philadelphia: Mosby, 2001: 21–5.
5. Di Benedetto P, Bertini L, Casati A, Et Al. A New Posterior Approach to the Sciatic Nerve Block: A Prospective, Randomized Comparison with the Classical Posterior Approach. *Anesth Analg* 2001; 93: 1040–4.
6. Auroy Y, Benhamou D, Bargues L, Et Al. Major Complications of Regional Anesthesia in France: The SOS Regional Anesthesia Hotline Service. *Anesthesiology* 2002; 97: 1274.
7. J.M. Richman, S.S. Liu. Et Al.: Does Continuous Peripheral Nerve Block Provide Superior Pain Control to Opioids? A Meta-Analysis. *Anesth Analg* 2006; 102:248-257.
8. Fanelli G, Casati A, Chelly JE, Bertini L. *Blocchi Periferici Continui*. Guida Pratica Illustrata. Milano: Mosby Italia. 2001.
9. Chelly JE, Geebhard R Et Al. Local Anesthetic PCA Via A Femoral Catheter for the Postoperative Pain Control of SN ACL Performed as an Outpatient Procedure. *AM J Anesthesiol* 2001; 28: 192-194.
10. Santorsola R, Casati A, Cerchierini E Et Al. Levobupivacaina Per I Blocchi Periferici Dell'Arto Inferiore: Un Confronto Clinico Con Bupivacaina E Ropivacaina. *Minerva Anestesiologica* 2001;67: 33-6.
11. Casati A, Borghi B, Fanelli G, Montone N, Rotini R, Frascini G, Vinciguerra F, Et Al. Interscalene Brachial Plexus Anesthesia and Analgesia for Open Shoulder Surgery: A Randomized, Double-Blinded Comparison Between Levobupivacaine and Ropivacaine. *Anesth Analg*. 2003;96(1):253-9.
12. Casati A, Vinciguerra F, Cappelleri G, Aldegheri G, Grispigni C, Putzu M, Et Al. Levobupivacaine 0.2% OR 0.125% for Continuous Sciatic Nerve Block: A Prospective, Randomized, Double-Blind Comparison with 0.2% Ropivacaine. *Anesth Analg* 2004;99(3):919-23.
13. Ben D, Bruce MD, Et Al. Analgesia After Total Knee Arthroplasty: Is Continuous Sciatic Blockade Needed in Addition to Continuous Femoral Blockade? *Anesth Analg* 2004;98:747-49.
14. Klein S; Grant SA, Greengrass RA, Nielsen KC, Speer KP, White W, Et Al. Interscalene Brachial Plexus Block with A Continuous Catheter Insertion System and a Disposable Infusion Pump. *Anesth Analg* 2000;91(6):1473-1478.

15. Sukhani R, Candido K, Doty R, Et Al. Infragluteal-Parabiceps Sciatic Nerve Block: An Evaluation of a Novel Approach Using a Single-Injection Technique. *Anesth. Analg* 2003;96(3),868-873.

16. Dadure C, Acosta C, Capdevila X. Perioperative Pain Management of a Complex Orthopedic Surgical Procedure with Double Continuous Nerve Blocks in a Burned Child. *Anesth Analg* 2004;98(6);1653-1655.

17. Ilfeld B, Morey T, Wang RD, Enneking FK. Continuous Popliteal Sciatic Nerve Block for Postoperative Pain Control at Home: A Randomized, Double-Blinded, Placebo-Controlled Study. *Anesthesiology* 2002; 97(4),959-965.

NEUROMONITORING AND DEPTH OF ANAESTHESIA

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What is the consciousness and what is it that we want to measure during anesthesia? Is the consciousness “to be awoken and able to respond to stimuli” and the contrary “to be anesthetized”? Consciousness supports a large number of activities of central nervous system such as decision making, learning, adaptation, problem solving and much more: we can't measure them during anesthesia! We can measure some physiological parameters such as brain electrical activity (1). It has been demonstrated that unconscious processing of stimuli involves brain areas including sensory cortex (prefrontal, parietal, medial temporal): for these parameters no commercial monitoring is available. The electroencephalogram (EEG) represents the rhythmic oscillations of voltage determined by synchronization of postsynaptic potentials of neurons and is controlled by interaction of limbic system, brain stem, thalamus and cortex. It is well known from 1875 that EEG varies during chloroform anesthesia (2). The EEG monitoring is a non-invasive measure and its changes are correlated with metabolic rate and cerebral blood flow (3); unfortunately, different anesthetics and analgesics produce different effects on EEG so it is difficult to determine the depth of anesthesia. In fact, the basic components of general anesthesia are analgesia and hypnosis, but they cannot be distinguished by EEG. Analgesic reduces the necessity of hypnotic but the opioids are not able to produce a full general anesthesia (4).

Evoked responses are the expression of the integrity of all structures and pathways to transfer the stimulus to

cerebral cortex. Midlatency auditory evoked potentials (MLAEP) change by changing depth of anesthesia because general anesthesia alter thalamic and cortical processing involved in mechanisms of consciousness (5).

EEG, processed EEG (i. e. Bispectral Index or Bis, Entropy) or Evoked Responses (i.e., MLAEP): it has not been clearly defined which one should be employed among these monitors.

The theories of mechanisms of anesthesia, at present, suggest that anesthesia is caused by the action of drugs on a variety of receptors and neuronal system (6). The consciousness is the product of the balance of the neurotransmitters and anesthetic drugs alter it: unbalanced neurotransmission change the EEG parameters with loss of synchrony. It has been supposed that the EEG based monitors can reflect different levels of information dissociation (desynchronization) and, therefore, are unable to assess the depth of anesthesia (7).

The ideal monitor of depth of anesthesia should be, with high sensitivity and specificity, able to point out the changes dependent by the state of consciousness. At present, there is still debate about whether these devices can provide valid informations on the depth of anesthesia or of hypnosis and on brain mechanisms mediating consciousness and anesthesia (8).

Bibliography:

1) Seth AK, Baars BJ & Edelman DB. Criteria for consciousness in humans and other mammals. *Consciousness and Cognition* 2005; 14: 119–139.

2) Caton R. The electrical currents of the brain. *British Medical Journal* 1875; 2: 278.

3) Veselis RA, Reinsel RA, Feshchenko VA & Dnistrian AM. A neuroanatomical construct for the amnesic effects of propofol. *Anesthesiology* 2002; 97: 329–337.

4) Wynands JE, Wong P, Townsend GE et al. Narcotic requirements for intravenous anesthesia. *Anesthesia & Analgesia* 1984; 63: 101–105.

5) Plourde G. Auditory evoked potentials and 40-Hz oscillations. *Anesthesiology* 1999; 91: 1187–1189.

6) Scholz J, Tonner PH, Krause T et al. Interactions of intravenous anesthetics with cerebral alpha-2-adrenoceptors. *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1999; 34: 642–647.

7) Mashour GA. Consciousness unbound: toward a paradigm of general anesthesia. *Anesthesiology* 2004; 100: 428–433.

8) John ER & Prichep LS. The anesthetic cascade: a theory of how anesthesia suppresses consciousness. *Anesthesiology* 2005; 102: 447–471.

REMIFENTANIL AND TIVA: PRESENT USE AND POSSIBILITIES FOR FUTURE APPLICATIONS

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The pharmacokinetic properties of remifentanyl are profoundly different from other opioids. There are two consequences of the very rapid metabolism. First, remifentanyl does not accumulate, even with very prolonged delivery. Second, remifentanyl has very little subject-to-subject variability. Thus, the offset of remifentanyl is not only rapid, but it is reliably rapid.

The anesthetic state is typically induced with a combination of opioid and hypnotic drug effect. One can think of the opioid effect as attenuating the painful stimulation that arrives from the periphery. The noxious stimulation that “gets past” the opioid filter is blocked upstream by suppressing consciousness, the effect of the hypnotic drug. Within this framework, one can give a small amount of opioid, in which case a large dose of hypnotic must be given to maintain an anesthetic state. Alternatively, one can give a large amount of opioid, in which case a modest amount of hypnotic is required. The choice is typically dictated by the relative pharmacokinetic properties of the two drugs. The offset of propofol is substantially faster than fentanyl, alfentanil, or sufentanil. Thus, older opioids are typically administered in modest doses and relatively large doses of propofol to needed maintain the anesthetic state. However, the pharmacokinetics of remifentanyl are much faster than those of propofol. Thus, when remifentanyl is combined with propofol, the logical approach is to shift the opioid-hypnotic balance to favor higher opioid concentrations, and lower hypnotic concentrations. Indeed, emergence from propofol-remifentanyl is remarkably fast when the drugs are used in this manner.

One possible complication of this approach is opioid induced hyperalgesia. There are data that high doses of opioids increase the relative sensitivity of individuals to noxious stimulation. It is difficult to separate acute hypersensitivity from acute tolerance, but the clinical questions to focus on are 1) is this effect real, 2) if it is real, does it have any clinical significance, 3) is it unique to remifentanyl, and 3) can it be modified?

The talk will focus on answering these questions. However, if you can't attend the lecture:

1) Opioid induced hyperalgesia is readily produced in animal models. Human evidence is still accumulating. It appears more with mechanical nociceptive pathways than with thermal nociceptive pathways,

2) The clinical significance is unclear.

3) It has been demonstrated with fentanyl as well as remifentanyl. The reason that most studies use remifentanyl is that remifentanyl can be given in huge doses without exposing the patient or volunteer to prolonged opioid drug effect.

4) NMDA antagonists (e.g., ketamine, d-methadone) appear to block the development of opioid induced hyperalgesia. Early studies suggested that low-dose naloxone infusions might be helpful, but subsequent studies failed to confirm these results.

The talk will also discuss what would be required for a remifentanyl patient controlled analgesia device. Remifentanyl has unique properties for a PCA device, but only if the pharmacokinetic behavior is used to best advantage. Otherwise, the same complications that functionally preclude remifentanyl use in the PACU will render remifentanyl unsuitable for PCA.

PHARMACOKINETICS MADE SIMPLE?

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Intravenous drug administration to provide anaesthesia has evolved considerably in the last decade and has become a popular alternative to inhalational anaesthesia in many countries. This evolutionary process has been the result of improved understanding of pharmacokinetics, pharmacodynamics, and the interactions which take place during drug administration. The greater use of intravenous techniques for anaesthesia has also led in turn to improved understanding of what underlies the actions of these drugs.

Better understanding of these processes has facilitated the development of computerised drug administration systems and allowed optimal drug selection and combinations. New intravenous drug delivery systems allow anaesthetists to vary anaesthetic depth in response to clinical signs in a manner intuitively similar to conventional volatile systems, thus simplifying the administration of intravenous anaesthesia.

The lecture will demonstrate how we can improve our understanding of the drugs and processes involved in intravenous administration by using an interactive programme which was developed specifically for this task by members of the European Society for

Intravenous Anaesthesia. A demonstration version of the TIVA Trainer software can be downloaded from the EuroSIVA web site at www.eurosiva.org. Drugs which are used commonly in anaesthesia will be examined using this software and the underlying factors which explain their pharmacokinetic activities will be discussed.

THE FUTURE OF MODEL BASED DRUG ADMINISTRATION: BRINGING IT ALL TOGETHER

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Quality control of anesthesia has become very important, owing the evolution in peri-operative management. Changes in surgical conditions and patient populations make it more than ever essential to manage anesthesia in a fast, simple and safe way. Hereby, a wide spectrum of pharmacological actions (analgesia, hypnosis, and suppression of somatic and autonomic responses to noxious stimuli) are needed to control the general anesthetic state 1. The ultimate goal when administering a particular dose of an anesthetic or analgesic drug is to obtain the desired clinical effect, for which a specific therapeutic concentration of the drug at the site of action (= the receptor) is required. Individual anesthetics gives a unique spectrum of pharmacological actions, so the concept of a common depth of anesthesia may need to be revisited to reflect the separate clinical components of the ideal anesthetic state 2. To reach these high standards of care, an optimal titration of both anesthetic and analgesic drugs is required. Classically, opiates are used to manage nociception and short acting hypnotics are widely used to titrate the hypnotic component of anesthesia. Due to various economical and pharmacological reasons³, most adult patients are induced used a single bolus of a short acting intravenous hypnotic drug (mostly propofol) followed by administering a short acting inhaled anesthetic. However, by optimizing drug administration techniques, economics might become more beneficial for TIVA. Target controlled infusion might help.

When optimizing the balance between hypnotic and analgesic action, the primary concern is to ensure an accurate level of the hypnotic component of anesthesia. When using inhaled drugs, a therapeutic concentration should be maintained accurately without creating side effects. Both awareness caused by too light anesthesia as hemodynamic side-effects caused by a too excessive anesthetic depth should be avoided. As such, the dose-response relationship has to be optimized.

Nowadays, various technical and pharmacological knowledge has been introduced into clinical practice to reach this target. First, better monitoring of the therapeutic effects has become available thanks to the introduction of hypnotic effect monitors. As this equipment measures cerebral drug effect, it has to be considered as an integral part of anaesthetic pharmacology. For the first time in the history of the specialty, anesthesiologists are able to differentiate and measure the various anaesthetic drug effects, being hypnosis and analgesia, by specific effect monitors. However, much work has still to be done. Various commercially available systems exists, but not all of them are validated to the same extend and therefore, all monitors should be validated as a measure of cerebral drug effect. Next to this, validation on clinical endpoints such as loss and return of consciousness is required. Clinical utility should be proven and finally, patient outcome should be enhanced by applying this new technology. For some of these monitors, some of these goals are already reached and published in the literature. For others major research is still required 4. Next to the availability of clinical effect monitors, optimal drug administration has become possible for both intravenous and inhaled anesthetics. The introduction of a wide range target-controlled administration of inhaled anesthetics targeting the end-tidal concentration 5 and target controlled infusion pumps for intravenous anesthetics has made it possible to fasten up administration closer to its therapeutic concentrations at the side of drug action, called the "effect-site concentration". It is already possible in clinical practice to combine both sources of dose-response information, being the concentrations and hypnotic effect monitors, to guide hypnotic drug administration. Proof exists that the combined information offers a higher degree of care 6.

When an accurate level of the hypnotic component of anesthesia is ensured, an optimal control of analgesia during surgical anesthesia is required too. Therefore, the noxious stimulus should be identified properly and blocked at the spinal level. Classically, this can be done by using opioids and/or locoregional anesthetic techniques. Recently, new properties of inhaled anesthetics at the spinal cord level have been observed and might be an alternative way to avoid ascending stimuli reaching the cerebral cortex; hereby causing an arousal reaction 7-9. If next to the hypnotic drug, an opioid is used, the interaction between both has to be considered. Most detailed, the study of this interaction can be done by using response surface methods. For the intravenous drugs, hypnotic-opiate balance has been published¹⁰⁻¹². Recently, Sandeep et al. ¹³ has studied the interaction between sevoflurane and remifentanyl. Response surface pharmacodynamic interaction models were built using the pooled data for sedation and

analgesic endpoints. Next to hypnotic-opioid interaction, one has to consider an interaction between two hypnotics. This interaction has to be understood by the clinician, as classically an intravenous induction bolus is given followed by an inhaled drug for hypnotic maintenance. Recently, others found that the interaction of propofol and sevoflurane on loss of consciousness and movement to skin incision during general anesthesia was additive, not synergistic 14.

In the nearby future, all sources of pharmacological and effect monitoring will be combined into anesthetic advisory and feedback systems enlarging the existing kinetic-based administration technology towards a total coverage of the dose-response relation. By measuring the patients' individual response to a certain given drug dose, drug administration could be guided by a pharmacodynamic advisory system estimating the complete dose-response relation. Additionally, when technology are found to be validated enough, closed-loop technology could be used. Closed-loop systems are able to make decision on their own and try to reach and maintain a preset target. As a result, they might help the anesthesiologist in optimizing the titration of drug administration without overshoot, controlling physiological functions and guiding monitoring variables.

References :

1. Kissin I: General anesthetic action: an obsolete notion? [editorial]. *Anesth Analg* 1993; 76: 215-8
2. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; 86: 836-47
3. Struys MM, Somers AA, Van Den Eynde N, Herregods LL, Dyzers D, Robays HM, Mortier EP: Cost-reduction analysis of propofol versus sevoflurane: maintenance of anaesthesia for gynaecological surgery using the bispectral index. *Eur J Anaesthesiol* 2002; 19: 727-34
4. Bruhn J, Myles PS, Sneyd R, Struys MM: Depth of anaesthesia monitoring: what's available, what's validated and what's next? *Br J Anaesth* 2006; 97: 85-94
5. Struys MM, Kalmar AF, De Baerdemaeker LE, Mortier EP, Rolly G, Manigel J, Buschke W: Time course of inhaled anaesthetic drug delivery using a new multifunctional closed-circuit anaesthesia ventilator. In vitro comparison with a classical anaesthesia machine. *Br J Anaesth* 2005; 94: 306-17
6. Struys MM, Jensen EW, Smith W, Smith NT, Rampil I, Dumortier FJ, Mestach C, Mortier EP: Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth: a comparison with bispectral index and hemodynamic measures during propofol administration. *Anesthesiology* 2002; 96: 803-16
7. Antognini JF, Carstens E: Isoflurane blunts electroencephalographic and thalamic-reticular formation responses to noxious stimulation in goats. *Anesthesiology* 1999; 91: 1770-9
8. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain [see comments]. *Anesthesiology* 1993; 79: 1244-9
9. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; 78: 707-12
10. Vuyk J: Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. *J Clin Anesth* 1997; 9: 23S-26S
11. Mertens MJ, Engbers FH, Burm AG, Vuyk J: Predictive performance of computer-controlled infusion of remifentanyl during propofol/remifentanyl anaesthesia. *Br J Anaesth* 2003; 90: 132-41
12. Nieuwenhuijs DJ, Olofsen E, Romberg RR, Sarton E, Ward D, Engbers F, Vuyk J, Mooren R, Teppema LJ, Dahan A: Response surface modeling of remifentanyl-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* 2003; 98: 312-22
13. Sandeep CM, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: Opioid-volatile anesthetic synergy: a response surface model with remifentanyl and sevoflurane as prototype. *Anesthesiology* 2006; 105: 267-278
14. Harris RS, Lazar O, Johansen JW, Sebel PS: Interaction of propofol and sevoflurane on loss of consciousness and movement to skin incision during general anesthesia. *Anesthesiology* 2006; 104: 1170-5

INTERACTIONS MADE SIMPLE

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"Make everything as simple as possible, but not simpler." Albert Einstein. Except for a few limited clinical circumstances where one drug alone is sufficient (e.g., a volatile agent), "modern" anaesthesia is at least a two drug process consisting of an opioid and an hypnotic agent. Propofol and volatile anesthetics alone cannot reliably prevent hemodynamic responses to noxious stimuli even when the pre-stimulus hemodynamic variables are depressed to an unacceptable degree. Opioids alone are not complete anesthetics because they

cannot reliably produce unconsciousness. The “modern” anaesthetist typically uses multiple drugs to achieve the anaesthetised state; benzodiazepines, thiopentone, propofol, opioid analgesics, nitrous oxide (still?), volatile anaesthetic agents, neuromuscular blockers, other analgesics adjuncts, antibiotics, reversal agents, sympathomimetics and autonomic nervous system blockers, among many others. Therefore, the potential for drug interactions is high.

Drug interactions can take several forms:

* Physicochemical interactions occur when the physical properties of the interacting drugs are somehow incompatible.

* Pharmacokinetic interactions occur when one drug somehow alters the disposition of another drug.

* Pharmacodynamic interactions occur when one drug somehow augments or reduces the effect of another drug.

Although it is not always well appreciated, anaesthetists routinely take advantage of the profound pharmacodynamic synergy between opioids and hypnotic agents. These synergistic combinations can be advantageous, because it is possible to achieve the therapeutic goals with fewer side effects and more rapid recovery.

This presentation will focus on understanding pharmacodynamic interactions between two agonists. In particular, emphasis will be placed on understanding isobolograms and response surfaces.

A more complete handout is available at URL:

<http://pkpdtools.com/downloads/pdf/interactions.pdf>

WHY IS IT USEFUL TO MEASURE HYPNOSIS?

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The primary goal of general anaesthesia is to ensure loss of consciousness during surgery. Nonetheless our ability to accurately assess adequacy of anaesthesia, and guarantee unconscious remains limited. The clinical observations used to assess anaesthetic adequacy all lack sensitivity and specificity for the presence or absence of consciousness.[1] Measurements of end-tidal volatile anaesthetic agent concentrations provide reassurance that the patient is receiving some anaesthetic agent, but provide only limited information about the likely adequacy of anaesthesia, since there is broad variability in the dose required for loss of consciousness.[2]

There is growing evidence of dose-related harmful effects of anaesthetic agents.[3] and some evidence that

excessive anaesthetic doses contributes to mortality rates.[4] Thus excessive anaesthesia is harmful and undesirable, and measurement of hypnosis for the purpose of avoiding excessive anaesthesia must benefit the patient.

Inadequate anaesthesia resulting in awareness with recall occurs in approximately 0.18% of patients undergoing general anaesthesia.[5] Since a large proportion of victims will suffer severe adverse psychological effects, [6,7] the 80% reduction in the incidence of awareness associated with BIS monitoring provides another strong argument for measuring hypnosis.[8]

References:

1. Russell IF. *Br.J.Anaesth* 1993;70:42-46
2. Chortkoff BS et al. *Anesth Analg* 1995;81(4):737-43
3. Xie Z et al. *Anesthesiology* 2006;104(5):988-94
4. Monk TG et al. *Anesth Analg* 2005;100(1):4-10
5. Sandin RH et al. *Lancet* 2000;355(9205):707-11
6. Osterman JE et al. *Gen Hosp Psychiatry* 2001;23(4):198-204
7. Lennmarken C et al. *Acta Anaesthesiol Scand* 2002;46(3):229-31
8. Myles PS et al. *Lancet* 2004;363(9423):1757-63

AWARENESS

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Although unconsciousness cannot be determined directly, the response to stimuli (i.e., surgical manipulation or verbal) can be measured. Thus, the depth of anaesthesia is determined by the balance between the stimulus, the response, and the drug concentration. In some instances the patient may recall intraoperative events, the so-called “explicit memory”. These events are rare. More often “intrinsic (or implicit) memory” may occur and it is defined by a response to an auditory input that is not consciously remembered after anaesthesia.

Recent studies have highlighted the significance of awareness in the anaesthetic practice: a Scandinavian trial found a rate of awareness between 0,1 and 0,18 % (1, 2) while previous studies had found a rate between 0,2 and 0,4 (3). Awareness is a potential risk for patient

morbidity including emotional distress and post-traumatic stress disorder (PTSD) (4). Perception of pain or surgical manipulations can lead to post traumatic stress disorders similar to those seen in victims of trauma or war.

Traditional clinical monitoring modalities during anesthesia are ineffective in preventing awareness. For instance, hypertension and tachycardia are generally not associated with report of awareness (5) and so is end-tidal anesthetic concentration monitoring (6). Several methods have been described to determine if a patient is still responsive under general anaesthesia. Inadequate depth of anaesthesia or awareness occurs in different situations. As an example a monitor that prohibits the occurrence of awareness during anaesthesia may not necessarily prevent movements, which are caused on the spinal level. It has been demonstrated that there is no strong correlation between the ability to respond to command and memory formation (7); it has also demonstrated that anatomic substrates of implicit memory exist (8) and that implicit memory can occur even if consciousness is not present (9). The incidence of implicit memory has been debated and can occur in patients with BIS values between 40 and 60 (10).

Recently, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has published a Sentinel Event Alert on anaesthesia awareness and concluded that awareness is under-recognized and under-treated in health care organizations; their recommendations include the use of neuromonitoring. Some support that the incidence of awareness may even increase with the use of neuromonitoring because patients are easily kept at reduced dosing in order to diminish side effects and wasteful anaesthetic consumption, without taking into account the increase of risk for patients to be aware or, in contrast, a value of monitor (i.e., BIS value of 40) that would result in a not deep anesthesia!

In conclusion, the awareness is a problematic of all general anesthesia independently from the anesthesia technique (Total IntraVenous Anesthesia or Inhalatory Anesthesia).

Bibliography:

- 1) Sandin RH, Enlund G, Samuelsson P, et al. Awareness during anaesthesia: a prospective case study. *Lancet* 2000;355:707–11.
- 2) Sebel PS, Bowdle TA, Ghoneim MM et al. The Incidence of Awareness During: A Multicenter United States Study. *Anest Analg* 2004; 99: 833-9.
- 3) Liu WHD, Thorp TAS, Graham SG, et al. Incidence of awareness with recall during general anaesthesia. *Anaesthesia* 1991;46:435–7.

4) Salomons TV, Osterman JE, Gagliese L, et al. Pain flashbacks in posttraumatic stress disorder. *Clin J Pain* 2004;20:83–7.

5) Domino KB, Posner KL, Caplan RA, Cheney FW. Awareness during anesthesia. *Anesthesiology* 1999;90:1053–61.

6) Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. *Lancet* 2000; 355:707–11.

7) Drummond JC. Monitoring depth of anesthesia: with emphasis on the application of bispectral index and the middle latency auditory evoked response to the prevention of recall. *Anesthesiology* 2000; 93: 876–882.

8) Schacter DL. The cognitive neuroscience of memory: perspectives from neuroimaging research. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 1997; 352: 1689–1695.

9) Veselis RA. Memory function during anesthesia. *Anesthesiology* 1999; 90:648-650.

10) Lubke GH, Kerssens C, Phaf H & Sebel PS. Dependence of explicit and implicit memory on hypnotic state in trauma patients. *Anesthesiology* 1999; 90: 670–680.

HEMODYNAMIC EFFECTS OF DEXMEDETOMIDINE SEDATION ARE INDEPENDENT OF AGE IN CHILDREN

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Background/Aims: This is the first large scale study that uses prospectively collected data to evaluate the hemodynamic and electrocardiogram effects of dexmedetomidine in children.

Methods: At our institution, dexmedetomidine is the standard of care for sedation for computerized tomography (CT) imaging. All children have a baseline set of vital signs prior to sedation which include MAP, oxygen saturation, heart rate and respiratory rate. An initial loading dose of 2 mcg/kg IV dexmedetomidine is administered over a 10 minute period. After the initial loading dose, the maintenance infusion of 1 mcg/kg/hr is initiated until completion of study. Detailed quality assurance (QA) data sheets document adverse events, hemodynamic and electrocardiogram data.

Results: 222 patients with mean age 2.9 years (range 0.1 – 10.6 years) received dexmedetomidine. Data were analyzed for different age groups. Repeated-measures ANOVA revealed that the profiles for each age group

demonstrated significant decreases in heart rate and blood pressure relative to pre-sedation values ($F = 189.38$, $P < 0.001$ and $F = 36.94$, $P < 0.001$, respectively), although the tests of slope of these changes were similar between age groups for heart rate ($F = 1.54$, $P = 0.15$) and blood pressure ($F = 1.65$, $P = 0.18$). No children were treated for hemodynamic instability and none exhibited hemodynamic changes outside of the age adjusted norms.

Conclusion:

Dexmedetomidine can cause fluctuations in heart rate and blood pressure which are independent on age and are clinically nonsignificant for most children.

REMIFENTANIL: MINTO'S MODEL ADAPTED FOR TIVA

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Remifentanil has already been used for some years, both in operating rooms and in I.C.U.s by means of continuous intravenous infusions. Such infusions can be delivered using:

- infusion pumps guided by microprocessors, containing Minto's model in the software for continuous infusion of Remifentanil in T.C.I. mode, or
- traditional infusion pumps, that can be operated "manually", and therefore in ml per hour (which are already obsolete), or in mg/Kg/min, mg/Kg/hour, mcg/kg/min etc; this method of infusion is defined as T.I.V.A. (Total Intra Venous Anaesthesia).

T.C.I. pumps are still not as widespread as those used for T.I.V.A. Delivering Remifentanil using infusion pumps for T.I.V.A does not allow the anaesthesiologist to know the concentration of the drug obtained at the effect site because with the same speed of infusion such concentrations vary noticeably from one individual to another, depending on gender, age, height and weight.

In order to standardize the use of Remifentanil using the T.I.V.A. mode if pumps that work in the T.C.I. mode are not available either in the operating rooms or in the I.C.U.s, we prepared a set of tables that indicate the effect site concentration of Remifentanil obtained in individuals differing in age, height, gender and weight, when the drug is infused at 17 different constant speeds. In order to construct such tables we have used one of the pharmacokinetic simulators, currently available and widely used around the world, TIVAtainer (F. Engbers, N. Sutcliffe and G. Kenny) version 8 build 5 (1). We simulated the infusion of Remifentanil at 17 different constant speeds, in 576 individuals, with different

heights, weights, genders and ages. Using the data collected, we constructed 36 tables to be referred to in order to calculate the appropriate speed of delivery of the drug for each patient, to obtain the desired effect site concentration at steady state, with an acceptable margin of error, in accordance with Minto's pharmacokinetic model (2, 3). This work is based on the supposition that the pharmacokinetic behaviour of Remifentanil is comparable in similar individuals and that the concentration obtained at the effect site will not be very different from that which is set out in Minto's model, if the parameters of the patient are not dissimilar to those in the table.

Introduction: The aim of this work is to present a method which allows the anaesthesiologist to know, to a good degree of accuracy, the concentration of remifentanil that has reached the effect site in patients who receive the drug by traditional infusion pumps (T.I.V.A. mode, mcg/Kg/hour). Delivering the remifentanil at a constant infusion speed leads to different site effect concentrations of the drug at steady state, in patients differing in age, height, weight and gender (2, 3).

Table 1, prepared using TIVAtainer, shows some examples of the different concentrations obtained using the same delivery speed of 0.5 mcg/Kg/min in different patients.

Note, for instance, that the concentration reached is 9.2 ng/ml in a male, weighing 50 Kg and 170 cm in height; and is 30,3 ng/ml in a female, 110 Kg in weight, 160 cm in height.

The difference in the concentrations obtained is 21,1 ng/ml, which is more than 300% higher in the second case, even if the speed of delivery is the same!

Table 1. Examples showing the great difference in steady state effect site concentration of remifentanil reached following a constant infusion rate of 0.5 mcg/Kg/min, in individuals differing in height, weight, age and gender, as indicated by Minto's model. The data are calculated using the pharmacokinetic simulator TIVA trainer. The steady state concentration of the drug is not the only characteristic that varies noticeably in patients differing in height, weight, age and gender, as per Minto's model. Also the length of the continuous constant infusion rate necessary to reach the steady state varies noticeably in different individuals. Using the TIVAtainer it is easy to realize, for instance, that when delivering remifentanil at a constant speed of 0.15 mcg/ml/min the time necessary to reach the steady state is 121 minute in a man of 20, weighing 50 Kg and 170 cm in height; and in another different individual, a 85 year old female, weighing 110 Kg, and 160 cm in height, that the time is 149' minutes. Furthermore, using the TIVAtainer it is possible to observe another important

clinical and practical aspect of the continuous constant speed infusion of remifentanyl, namely 24 minutes of continuous constant infusion, following Minto's model, will determine an effect site concentration which is at least 90% of the steady state concentration.

Even in particular cases, for instance, of very old and overweight patients (still within the range considered in Minto's studies: 20-85 years old and 45-110 Kg) (2,3), where the time to reach the steady state concentration is much longer than in other people, 90% of the steady state concentration is reached in a relatively short period of 24 minutes or less of continuous infusion. Some examples are reported in table 2.

Table 2: in individuals differing in height, weight, age and gender, as indicated by Minto's model, both the effect site concentration reached at steady state and the time necessary to reach the steady state concentration vary noticeably, following a constant rate infusion, for instance 0.15 mcg/Kg/min (38 vs 362 minutes). In any case, however, the time necessary to reach 90% of that concentration is 24 minutes or less.

In the columns the following values are shown: weight in Kg, height in cm, age in years, gender, steady state effect site concentration in ng/ml, time to reach the steady state concentration in minutes, 90% of the steady state effect site concentration in ng/ml, time to reach 90% of the steady state concentration in minutes.

Materials and methods: This work is based on the observation that in patients of any age, height, weight and gender, according to Minto's model, at least 90% of the steady state effect site concentration of remifentanyl will be reached after 24 minutes of constant rate infusion.

To find out the effect site concentration of the drug reached at steady state at different constant speed of delivery we used the pharmacokinetic simulator TIVAtrainer. With the data collected we constructed 36 tables to be referred to in order to calculate the appropriate speed of delivery of the drug for each patient and to obtain the desired effect site concentration at steady state, with an acceptable margin of error, in accordance with Minto's pharmacokinetic model. The 36 tables contain the data related to 576 human models, which differ from each other in weight, age, height and gender. Using these tables it is possible to pinpoint, in any one of the 576 different human models, the concentration of remifentanyl reached at the effect site after at least 24 minutes of continuous constant speed infusion, following Minto's model. We can find the data related to the effect site concentration reached in our patient to a good degree of accuracy by matching up the appropriate model. The 36 tables have been constructed referring to patients having the characteristics reported in table 3.

Table 3: Variables utilized to build 576 human models.

The 36 tables have been constructed simulating 17 different constant infusion speed, commonly used in clinical practice, indicated in table 4.

Table 4: 17 different constant infusion rates simulated in 576 different human models, to build the 36 tables.

Tables 5 : One of the 36 tables constructed using the data indicated in table 3 and the pharmacokinetic simulator TivaTrainer, simulating the 17 different constant infusion speeds indicated in table 4.

Results: For several months we have been using the tables in the operating rooms, in O.R.L., Urology and Plastic Surgery, to deliver remifentanyl using Fresenius Pilot A and Terumo pumps, in T.I.V.A. mode ($\mu\text{g/Kg/min}$), together with propofol or Desflurane. In these cases the quality of anaesthesia was similar to that of T.C.I. mode (rapid onset of pharmacodynamic effects, rapid adjustment of the depth of the anaesthesia and analgesia, rapid recovery) limiting the number of episodes of bradycardia/tachycardia and hypotension/hypertension as side effects connected to hypo- or hyper- dosage of the drug.

Discussion: The use of the 36 tables allows us to know with an acceptable degree of approximation the steady state effect site concentration of remifentanyl during a continuous infusion at constant rate, and seems to be a useful and simple tool to deliver that drug in T.I.V.A. mode (mcg/Kg/min), resembling the optimal way of delivering, the T.C.I.

Their use allows us to exploit the favourable pharmacokinetic characteristic of remifentanyl, reducing the number and the severity of the side effects due to unconscious hyper- or hypo- dosage. Furthermore, the tables allow even those who are not experienced with the use of T.C.I. mode, to become familiar with remifentanyl, a drug which has peculiar, favourable characteristics related to its effectiveness in all contexts and the rapidity of its kinetics, but which has to be properly delivered to avoid side effects due to hyper- or hypo- dosage. Knowing the effect site concentration, which is obtained to a good degree of accuracy using the tables described above, reduces the number of episodes of under- and over- dosage of the drug and the side effects related to them, and so even those who are not yet experienced in total intravenous anaesthesia can confidently approach this method of delivering remifentanyl with little risk for the patient.

Conclusion: When the T.C.I. pumps for remifentanyl are not available in the clinical practice (operating rooms or I.C.U.), the use of the 36 tables indicating the steady state effect site concentration at different speeds of constant continuous infusion rate, in individuals differing in weight, height, gender and age, enable us to

operate knowing with an acceptable degree of approximation at any time, the effect site concentration of the drug in our patient, thus limiting the risk of side effects due to the over- or under-dosage of the drug.

References:

1. F. Engbers, N. Sutcliffe, G. Kenny. Tivatrainer version 8 build 5. <http://www.eurosiva.org> or webmaster@eurosiva.org
2. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJM, Gambus PL, Billard V, Hoke JF, Moore KHP, Herman DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology* 1997; 86: 10-23
3. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanyl. II. Model application. *Anesthesiology* 1997; 86: 24-33

Continuous infusion speed 0.5 mcg/Kg/min				
Age Yrs	20	40	60	80
	Effect site concentration at steady state ng/ml			
Male; 50 Kg; 170 cm	9.2	10.5	12.1	14.4
Female; 70 Kg; 160 cm	12.7	14.4	16.5	19.5
Male; 90 Kg; 170 cm	14.6	16.3	18.5	21.4
Female; 60 Kg; 180 cm	10.8	12.2	14	16.5
Male; 85 Kg; 180 cm	13,6	15,2	17,2	19,8
Female; 85 Kg; 160 cm	15,1	17,1	19,6	23,1
Female; 110 Kg; 160 cm	19,7	22,3	25,7	30,3

Table 1

Constant Infusion Rate 0,15 mcg/Kg/min							
Kg	Cm	Yrs	M/F	Ce SS	T SS	Ce 90%	T 90%
50	170	20	M	2,8	121'	2,5	18'
70	180	25	F	3,8	197'	3,4	19'
80	190	40	M	4,3	91'	3,9	21'
90	170	60	F	5,9	64'	5,3	19'
110	160	85	M	8	109'	7,2	21'
110	160	85	F	9,5	149'	8,5	20'

Table 2

Weight Kg	Height cm	Age Yrs	Gender
50	150	20	M
60	160	30	F
70	170	40	
80	180	50	
90	190	60	
100	200	70	
		80	
		90	

Tabella 3

Infusion rate mcg/Kg/min
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.80
0.90
1.00

Table 4

Infusion rate mcg/Kg/min	80 Kg; 180 cm																							
	Male										Female													
	20 yrs	30 yrs	40 yrs	50 yrs	60 yrs	70 yrs	80 yrs	90 yrs	20 yrs	30 yrs	40 yrs	50 yrs	60 yrs	70 yrs	80 yrs	90 yrs								
0.05	1.3	1.4	1.5	1.5	1.7	1.8	1.9	2.1	1.4	1.4	1.5	1.6	1.7	1.9	2	2.2	1.4	1.4	1.5	1.6	1.7	1.9	2	2.2
0.1	2.6	2.7	2.9	3.1	3.3	3.5	3.8	4.1	2.7	2.8	3	3.2	3.5	3.7	4	4.4	2.7	2.8	3	3.2	3.5	3.7	4	4.4
0.15	3.9	4.1	4.4	4.6	5	5.3	5.7	6.2	4.1	4.3	4.6	4.9	5.2	5.6	6.1	6.6	4.1	4.3	4.6	4.9	5.2	5.6	6.1	6.6
0.2	5.2	5.5	5.8	6.2	6.6	7.1	7.6	8.3	5.4	5.7	6.1	6.5	6.9	7.5	8.1	8.8	5.4	5.7	6.1	6.5	6.9	7.5	8.1	8.8
0.25	6.5	6.9	7.3	7.7	8.3	8.8	9.5	10.3	6.8	7.2	7.6	8.1	8.7	9.3	10.1	11	6.8	7.2	7.6	8.1	8.7	9.3	10.1	11
0.3	7.8	8.2	8.7	9.3	9.9	10.6	11.4	12.4	8.1	8.6	9.1	9.7	10.4	11.2	12.1	13.2	8.1	8.6	9.1	9.7	10.4	11.2	12.1	13.2
0.35	9.1	9.6	10.2	10.8	11.6	12.4	13.3	14.5	9.5	10	10.7	11.4	12.2	13.1	14.2	15.4	9.5	10	10.7	11.4	12.2	13.1	14.2	15.4
0.4	10.4	11	11.6	12.4	13.2	14.2	15.2	16.5	10.8	11.5	12.2	13	13.9	15	16.2	17.6	10.8	11.5	12.2	13	13.9	15	16.2	17.6
0.45	11.7	12.4	13.1	13.9	14.9	15.9	17.1	18.6	12.2	12.9	13.7	14.6	15.6	16.8	18.2	19.8	12.2	12.9	13.7	14.6	15.6	16.8	18.2	19.8
0.5	13	13.7	14.6	15.5	16.5	17.7	19.1	20.6	13.6	14.3	15.2	16.2	17.4	18.7	20.2	22	13.6	14.3	15.2	16.2	17.4	18.7	20.2	22
0.55	14.3	15.1	16	17	18.2	19.5	21	22.7	14.9	15.8	16.8	17.9	19.1	20.6	22.2	24.2	14.9	15.8	16.8	17.9	19.1	20.6	22.2	24.2
0.6	15.6	16.5	17.5	18.6	19.8	21.2	22.9	24.8	16.3	17.2	18.3	19.5	20.8	22.4	24.3	26.4	16.3	17.2	18.3	19.5	20.8	22.4	24.3	26.4
0.65	16.9	17.9	19	20.1	21.5	23	24.8	26.8	17.6	18.7	19.8	21.1	22.6	24.3	26.3	28.6	17.6	18.7	19.8	21.1	22.6	24.3	26.3	28.6
0.7	18.2	19.2	20.4	21.7	23.1	24.8	26.7	28.9	19	20.1	21.3	22.7	24.3	26.2	28.3	30.9	19	20.1	21.3	22.7	24.3	26.2	28.3	30.9
0.8	20.9	22	23.3	24.8	26.4	28.3	30.5	33	21.7	23	24.4	26	27.9	29.9	32.4	35.2	21.7	23	24.4	26	27.9	29.9	32.4	35.2
0.9	23.4	24.7	26.2	27.8	29.7	31.8	34.3	37.2	24.4	25.8	27.4	29.2	31.3	33.6	36.4	39.6	24.4	25.8	27.4	29.2	31.3	33.6	36.4	39.6
1	26	27.5	29.1	30.9	33	35.4	38.1	41.3	27.1	28.7	30.5	32.5	34.7	37.4	40.4	44	27.1	28.7	30.5	32.5	34.7	37.4	40.4	44

Table 5

THE ANALYSIS OF REMIFENTANIL AND ITS MAJOR METABOLITES IN HUMAN CEREBRAL EXTRACELLULAR FLUID, BLOOD SAMPLES AND CSF SAMPLES

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Background and aims: The primary objective of this study is to measure remifentanyl and its major metabolites in brain interstitium, cerebral extracellular fluid (CSF) and whole blood samples and to compare these data with TCI infusion of remifentanyl and its value.

Methods: We will insert a microdialysis catheter (CMA 70) in the brain interstitium (2 cm inside the cortex) perfused by an infusional pump (0.03 ml/min) with a lactated Ringer's solution for 3 hours in 10 consecutive patients undergoing craniotomy for supratentorial mass lesions. The interstitial fluid in

equilibrium with the brain will be collected at the end of the central time (i.e., after dura closure (T1); average T0 (dura opening) -T1 length = about 3 hours). At the same time two samples will be drawn from plasma and CSF. For each patient, 7 samples will be drawn (Plasma + CSF basal after anaesthesia induction, plasma + CSF + brain interstitium at dura closure, and plasma + CSF at the end of the surgery) for a total of 70 samples. Total intravenous anesthesia will be guaranteed. It will be performed with Alaris ® TCI systems; the level of consciousness will be assessed with BIS ® systems.

Results: The purpose of the study will be to verify in vivo the mathematical hypothesis upon which TCI is based. In particular, we will test in vivo the effectiveness of plasmatic and effect site concentrations. It will be very interesting to consider, indeed, the correlation between the concentration of remifentanil in the brain and in the CSF.

Conclusions : In a previous study by Vuyk(1) and coll. plasma concentrations of remifentanil were evaluated. The results confirmed the previsions from a concentration of 0.1 to 19.6 ng ml⁻¹. The measured blood values of remifentanil obtained through the TCI device ranged from €“15 to +20% of the expected values calculated by using Minto(2)€“s method.

In our study the possibility to evaluate the concentration on the effect site (the brain interstitium) could be a real validation of Minto predictive scheme.

1) Br J Anaesth. 2003 Feb;90(2):132-41

2) Anesthesiology 1997; 86: 10-23

LIGHT TOTAL INTRA VENOUS ANESTHESIA (TIVA) IN VASCULAR SURGERY

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Introduction: The TIVA is now days an extended technique to perform a general balanced anesthesia. The association of a morphine like analgesic, a narcotic and a curare allows to obtain a correct result.

However when it is possible to avoid the curarisation, a general narco analgesia could be realized without difficult. And more over, if the narcotic associated to the analgesic is only used for the induction – intubation period, the maintenance can be obtained with only one intravenous drug. An only one IV anesthetic drug allows to avoid all the interferences of a products association, driven to a better understanding of the intra anesthetic

patient modifications, over all those concerning the cardio vascular status.

Focus in this objective, a Light TIVA technique, has been used in patient operated on, for cardio vascular intervention.

Patient: A total of 205 patients were anesthetized and non invasive hemodynamic monitored (Hemosonic 100.Arrow USA), for cardio vascular interventions. 65; 40 Men - 25 Women, 77±9Y.O., ASA II=57 and III=8, NYHA 1=12; 2=53. were operated on for an carotid endarterectomy. 93; 62 men – 31 women, 79 ±11Y.O., ASA II=48 and III= 45, NYHA 1= 8; 2=68; 3=17, were operated on for a peripheral artery by pass. 47; 18 Men - 29 Women, 48±19 Y.O., ASA I= 42 and II =5, NYHA 1=45; 2=2. were operated on for a varix operation.

Method: The protocol was adapted for the carotid endarterectomy to produce “conscious” light TIVA, allowing the control of the patient motility during the per operatory period. In this case the technique was the follow one: Pre oxygenation for 2 min. followed by a Remifentanil (REM) infusion 1 mcg/kg/min for 2 min. Then reduced to 0.5 mcg/kg/min. Propofol 1 mg/kg was injected. Intubation under glottis local anesthesia (5%lidocaïne spray). Ventilation with a FiO2 1, RR 12 c/min. and TV 8 ml/kg. The dose of REM was regulated to obtain a coordinated motor response at the anesthesiologist demand (max.1.5-min.0.15 mcg/Kg/min.).

For the other patients the same protocol was applied but the maintenance dose of Remifentanil was a stable one at 1.2 mcg/Kg/min. Ventilation was provide with O2/ Air at 50% each.

Results: The objective of anesthesia was reached in all the patients. The most common cardio vascular events observed were a bradycardia under 55/b/min (55%) corrected with atropine; a systolic arterial pressure under 90 mm Hg. 22 % and a hypertension over 170 mm Hg 12 %. Aortic blood flow was decreased (43%) during the bradycardia. The relationship between flow and resistances was relatively preserved. Remembering of peri operatory facts was encountered in 63 % of the carotid endarterectomy patients, 4 % in the varix patients and 2 % in the arterial by pass operations.

Discussion: With the light TIVA, the duration of anesthesia is not limited. The consciousness state allows a clinical evaluation of the clamping and declamping repercussions, in patient operated for a carotid endarterectomy. All the patients were under adequate mechanical ventilation. The hemodynamic monitoring modifications observed driven to an oriented and fast therapeutic intervention, without modification of the anesthetic protocol. The patients’ recovery was obtained in 6±2 min. after the Remifentanil perfusion stopped.

Only 4 % of nausea and 1 % of vomiting were observed.

The procedure seems to be interesting, not only for the carotid endarterectomy but even for patient at cardiovascular risks or for day hospital cases. However, the protocols proposed have to be carefully applied.

TCI OF PROPOFOL AND REMIFENTANIL FOR PERIOPERATIVE MANAGEMENT OF A SUPER-OBESE PATIENT: A CASE REPORT

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The first part of this lecture will deal with what obesity is, pre- and perioperative problems/risks that this particular class of patients poses to the anesthesiologist and anesthetic technique, while during the second part a video will be projected, and all the theoretic considerations will be put into practice.

Obesity is defined as an excess of fat tissue compared with normal values for an individual of the same age and gender. The international WHO classification of obesity is based upon the Body Mass Index (BMI), calculated as Total Body Weight (TBW) divided by the square of the height in meters. Obesity is defined as a BMI ≥ 30 kg/m², and morbid (or Class III) obesity as a BMI ≥ 40 kg/m². We report the case of a 40-year-old male, weight 198 kg, height 1.75 m, Body Mass Index (BMI) 64.7 kg/m², American Society of Anesthesiologists Physical Status III, scheduled for bilio-intestinal bypass surgery. A great deal of pathophysiological changes happen to the obese patient: the cardiovascular, respiratory, gastrointestinal and renal system are only a few examples. It is clear that some of these changes are likely to affect drug distribution and elimination. As a result, the first problem is to try to optimize drug choice. Unfortunately, this is not the only problem. In fact, securing the airway, preoxygenation, patient positioning, anesthetic induction, neuromuscular blockade and rapid emergence with a prompt return of airway protective reflexes are all critical points. All these aspects will be briefly reviewed in our lecture prior to decide the anesthetic technique. Patient's physical findings suggested the possibility of difficult airway management, thus an awake fiberoptic intubation was discussed with him. For their pharmacokinetic properties, propofol and remifentanyl seem to be particularly suitable for continuous infusion in morbidly obese patients. Therefore we opted for Target Controlled

Infusion (TCI) of propofol and remifentanyl both for conscious sedation-analgesia during awake fiberoptic nasotracheal intubation and for maintenance during the surgery, since TCI offers several advantages over non-pharmacokinetic-driven total intravenous anesthesia. Contrary to what some colleagues affirm, no change in weight input is needed for propofol, while some problems exist with remifentanyl. However, safe anesthesia can be provided anyway by titrating the drug to a particular clinical endpoint. This will be better explained in the lecture.

During the second part of this lecture, a video will be projected. We will review the critical aspects of managing a morbidly obese patient, as well as anesthetic choice, intubation, maintenance and emergence.

SERVIN FORMULA VS NO CORRECTION FOR WEIGHT INPUT IN TCI DEVICES DURING PROPOFOL-REMIFENTANIL TCI DURING BARIATRIC SURGERY

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Background: The WHO defines obesity as a BMI ≥ 30 kg/m², and morbid (or Class III) obesity as a BMI ≥ 40 kg/m². Due to their pharmacokinetic characteristics, propofol and remifentanyl seem to be particularly suitable for continuous infusion in morbidly obese patients. Moreover, the introduction of Target Controlled Infusion (TCI) gave the further potential to improve the accuracy in achieving and maintaining the desired level of anesthesia. Despite the fact that the kinetic set published by Marsh and colleagues is weight proportional, there is still some grade of uncertainty about the appropriate weight input when using a TCI of propofol in morbidly obese patients. In particular, many authoritative colleagues still suggest to correct the weight according to a formula used by Servin and colleagues in their study when the effect of obesity on propofol pharmacokinetics was not clear.

The purpose of this prospective, randomized, double-blind study was to determine the predictive performance of propofol TCI in morbidly obese patients when no weight correction had been used vs weight correction according to the formula used by Servin and colleagues in their study.

Methods: 22 patients (ASA II–III, age 25–60 yr, BMI 35–62) were randomly allocated to receive either a propofol TCI based on Servin's weight correction formula (Group Servin) or a propofol TCI with no

weight correction (Group TBW). Anesthesia was induced by propofol 6 µg ml⁻¹, which was subsequently adapted to maintain stable BIS values ranging between 40 and 50. Arterial blood samples were collected before starting the infusion and every 15 minutes thereafter to determine the predictive performance. During the maintenance of anesthesia, blood propofol target concentration was adapted to each patient's need, with a BIS value maintained between 40 and 50.

As for remifentanyl, using the patient's total body weight as weight input significantly overestimates plasma concentration, as will be noted during the lecture. This is why we used a method to correct Minto's pharmacokinetic set in our patients. However, target remifentanyl concentration was carefully titrated to a particular clinical endpoint, i.e. the maintenance of heart rate and blood pressure within ±10% of baseline values.

Results: Median performance error (MDPE) and median absolute performance error (MDAPE) were -31.27% and 31.27 % for Group Servin, -17.19% and 20.23% for Group TBW, respectively. Wobble median value was 7.52% for Group Servin and 8.47% for Group TBW, while divergence median value was -4.67% h⁻¹ for Group Servin and -4.59% h⁻¹ for Group TBW. As a result, weight correction causes a clinically unacceptable bias as for performance. MDAPE, wobble and divergence are not significantly different between the two groups.

Conclusions: Weight input should not be corrected whenever propofol TCI is used in morbidly obese patients. Even though the use of an unadjusted pharmacokinetic set partially eliminates the inaccuracies found when a weight correction is used, anesthesiologists should consider that in these cases an overestimation of real plasma concentration exists in morbidly obese patients, opposite to what happens in non-obese patients, in whom an underestimation is observed.

PROPOFOL TARGET IN A DIABETIC PATIENT

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Background and aims:

Propofol, for its pharmacokinetic characteristics, such as context-sensitive half-time and T_{1/2} Keo, represents the best intravenous hypnotic and reaches the prototype of an ideal intravenous anesthetic. These characteristics explain the quality of awakening from anesthesia and the

possibility to have rapid and safe modifications of the anesthetic plan.

The Target-Controlled Infusion (TCI) is an infusional system able to:

- keep constant propofol concentrations during a time period;
- to have a quick and reliable increasing or reduction of the plasmatic target concentrations;
- estimate the waking up times.

All this makes propofol a useful and safe drug for each anesthesiologic procedure.

However special care has to be observed, in relation to the excipients, especially the purified egg fosfatide and the glycerol, in patients with alterations of the lipidic metabolism (e.s. in the renal impairment, in the diabetes, in haepatic impairment) and in the other conditions in which it is necessary use caution in the lipidic emulsion administration (e.s. septicaemia). Furthermore in the diabetic patients submitted to surgical procedures we always find a stress reaction with increasing of the hyperglycemic hormones: cortisol, glucagone, growth hormone and catecolamines, with a consequent insulin level reduction. Cortisol, growth hormone and glucagone speed up gluconeogenesis, while the catecolamines support the haepatic glycogenolysis. The hormonal and metabolic reactions are directly connected to the stress entity, being lower in the minor surgery and higher in major surgery. It is generally recommended the monitoring of the plasmatic levels of lipids and glucose in patients with Propofol continuous infusion, especially in those at risk of lipidic and glycaemic overload.

Methods:

31 insulin-dependent diabetic patients, submitted to laparoscopic major surgery and then admitted to Postoperative Intensive Care, have been studied. In these patients a glycaemic control has been made with continuous CGMS® System Gold glycaemia monitoring since the evening before operation until discharge from Intensive Care after 48 hours. Patients have been submitted to major abdominal surgery for a minimum time of 2 hours (colic resections, gastrectomies, etc).

The anesthesiologic protocol is described (Tab1):

With the following monitoring:

- arterial pressure: SAP, DAP, MAP
- heart rate
- electrocardiography
- body temperature
- pulsoximetry

- central venous pressure
- capnometry
- emogasanalysis
- TOF watch
- BIS monitoring of the depth of anaesthesia
- diuresis

A glycaemic curve has been built in the subsequent 48 hours for all the patients, correcting the glycaemia with intravenous doses of Rapid-Acting Insulin.

Results:

Statistical analysis has been led with linear regression analysis.

Results (Tab. 2):

A linear regression of the glycaemic values has been discovered, beneath 110 mg/dl, between the target and the number of hours passed from the term of propofol infusion. This value is statistically significant ($r = r = 0,88$).

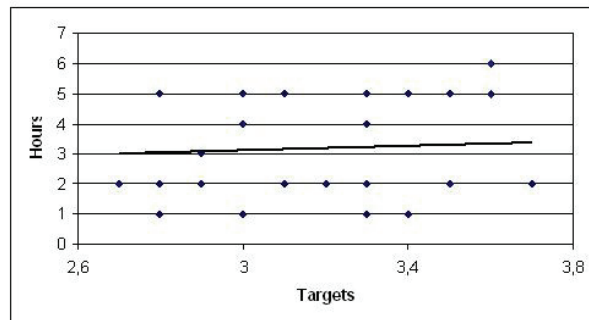
Such condition however has not verified in non-diabetic patients, where has not been discovered any linear regression ($r = 0,06$). (v). Tab.3) :

Conclusions:

We can therefore conclude from the preliminary data that Propofol target represents a determining element in the post-operative glycaemia monitoring only in diabetic patients submitted to major surgery.

References:

- 1) Mc Anulty GR, "Anaesthesia for the diabetic patient", BR J Anaesth, 2003 Apr 90(4):434-9
- 2) Dierdorf SF, "Anaesthesia for patient with diabetes mellitus", Curr Opin Anesth, 2002 Jun 15 (3) :351-7



Premedication

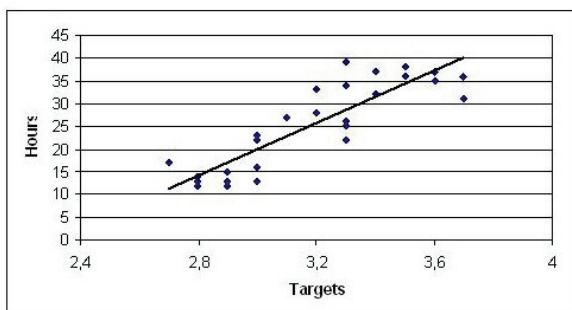
Atropine 0,01 mg/kg i.m.
 Midazolam 0,03-0,07 mg/kg i.m.

Induction

Propofol TCI 4 µg/ml
 Remifentanyl 0,25 µg/kg/min
 Cis-atracurium 0,20 mg/kg

Maintenance

O2 + Air
 Propofol TCI 2,7-3,7 µg/ml
 Cis-atracurium 0,04 mg/kg al 25% TOF



PROPOFOL PHARMACODYNAMIC EFFECT ON THE CEREBRAL STATE INDEX IN DOGS

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In this study, a nonlinear model was developed to describe the Cerebral State Index (CSI) of the EEG tendency during general anesthesia in dogs, by evaluating the effect of the anesthetic drug propofol. The model was based on a three compartmental model (Beths PK model), an effect compartment (developed in a parallel study) and a Hill Equation structure with individually identified parameters.

The clinical data were collected in 14 dog surgeries under TIVA using propofol. The data were independently used for modeling and testing, only during the induction phase. One model presented good results in all dogs, following the CSI trend. However, the model results presented a time delay between modeled CSI and real CSI trend, this delay was significantly correlated with baseline Mean Arterial Pressure (MAP) ($R=0.92$, $P<0.05$). This information was further incorporated into the model, allowing for individual dog adjustment.

The good performance of the developed model shows that the CSI follows the propofol effect-site concentrations. In addition, an initial model with fixed parameters could be adjusted to the individual characteristics of each dog (MAP). This is an important step to improve veterinarian surgical anesthesia since a stable anesthesia level is important to guarantee good surgical conditions. A model for drug-effect in veterinarian anesthesia is an important step when developing advisory, educational and control systems. The overall aim is to improve animal safety and comfort.

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REAL-TIME MONITORING OF PROPOFOL IN EXHALED BREATH DURING TARGET CONTROLLED TOTAL INTRAVENOUS ANESTHESIA (TCI-TIVA)

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Background:

Propofol is an aromatic compound with low water solubility and low vapor pressure. These properties allow diffusion through the alveolocapillary membrane and detection of propofol in exhaled breath of patients undergoing TIVA. The aim of this study was to quantify propofol in exhaled breath and to examine the relationship between propofol concentrations in exhaled breath and propofol whole blood levels in patients undergoing TCI-TIVA.

Materials and Methods:

Eleven adult patients received TCI-TIVA with propofol during neurosurgical procedures. For detection of volatile propofol a gas analyzer based on ion-molecule-reactions coupled with quadrupole-mass-spectrometry (IMR-MS) (1) was used. The system was directly connected to the endotracheal tube by a T-piece and 50ml/min of breathing gas were continuously analysed for propofol concentrations. Propofol whole blood levels were determined by liquid chromatography tandem-mass-spectrometry.

Results:

Propofol could be detected in exhaled breath of all patients. The correlation coefficient between expiratory breath concentrations and blood propofol levels within the whole sample was $r^2=0.72$ ($n=11$, 49 measurements, $p<0.001$). In individual patients, Pearson's correlation coefficients ranged from $r^2=0.62$ to $r^2=0.97$. Expiratory propofol levels followed changes in propofol whole blood concentrations within 60s.

Conclusions:

Analysis of propofol in exhaled breath by IMR-MS allows monitoring of relative changes in propofol whole blood concentrations. This could permit non-invasive routine estimation of propofol blood levels in patients undergoing TIVA similar to monitoring of MAC with volatile anesthetics. This may allow the development of closed-loop TCI devices.

Acknowledgements:

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RELIABILITY OF ENDTIDAL CO₂ MONITORING DURING PROPOFOL INFUSION SEDATION IN NEONATAL PATIENTS UNDERGOING SPECT

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Background:

Single photon emission computed tomography (SPECT) provides reliable measure of regional Cerebral Blood Flow. This procedure needs complete immobility of the patients. Sedation is essential in neonates undergoing SPECT. The aim of this study was to define the efficacy of EtCO₂ monitoring in neonatal patients undergoing SPECT under propofol infusion sedation.

Methods:

Fifteen patients undergoing SPECT for Moyamoya disease and Sturge-Weber syndrome, intracranial arachnoid cysts and epilepsy were included aged between 5 and 12 months and weighting between 6 and 15 Kg. After EMLA application, venous cannulation was performed and radioactive isotope was injected 1 hour before the examination. After the positioning on the SPECT table, propofol bolus 1,5-2 mg/Kg was administered and an infusion was started ranging between 10 and 3 mg/Kg/hr. Older children (>8 months) received also midazolam i.v. 0,05-0,07 mg/Kg. EtCO₂ added to standard monitoring was detected by a device (devited cannula by Salter Labs USA or microstream sampling line by Oridion) applied to children's nostrils.

Results:

All children showed stable cardiorespiratory parameters. Wake-up time was less than 4 minutes. No transient apnoea was noted during the procedures as the continuous measurement of EtCO₂ demonstrated. No PONV or agitation was observed in postoperative period.

Conclusions:

Propofol infusion administered by specialists is a safe technique even in neonates. Spontaneous ventilation is advantageous for optimizing time and parent comfort who believe that oro-tracheal intubation is more invasive. In agreement with recent reports, EtCO₂ was found to be effective to detect apnoea and hypoventilation even in neonates.

EFFECT OF TIVA WITH PROPOFOL/REMIFENTANIL ON NEUTROPHIL GRANULOCYTES FUNCTION IN PAEDIATRIC PATIENTS

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Background:

According to literature reports, postoperative complications, as nosocomial infections, could be due to neutrophil granulocytes alterations induced by lipophilic

drugs. We analyzed the metabolic function of granulocytes in paediatric patients undergoing ophthalmic surgery, using the biochemical test of chemiluminescence based on the emission of light by redox reaction as observed on the cells surface during phagocytosis.

Methods:

We enrolled nine patients, ASA I, age 9.1 +/- 2.5 yr undergoing strabismus surgery. After midazolam per os (0.5/0.75 mg/kg), anaesthesia was induced and maintained by propofol (8-6 mg/kg/hr) and remifentanyl (0.5-0.25 mcg/kg/min) titrated to maintain haemodynamic stability and a bispectral index (BIS) value of 40. Monitoring included NiBP, HR, SaO₂, EtCO₂. Blood samples were collected at different times (induction, end of anaesthesia, after 2 and 24 hr) and analyzed for measurement of chemiluminescence. The data were expressed as mean +/- standard deviation (SD). Intragroup comparison was made using student-t test. The threshold for statistical significance was p<0.05. Intergroup comparisons were evaluated using analysis of variance (ANOVA)

Results:

For each patient we obtained a value of chemiluminescence statistically greater from the baseline particularly in presence of reagents as luminol and zimosan increasing the intensity of weak chemiluminescence.

Conclusions:

Chemiluminescence parameters suggest an interaction between these drugs and neutrophil granulocytes compromising the scavenger activity of these immune system cells. We suppose that this interaction even though temporary and innocuous in healthy patients, could lead to a decrease of body's defences in pathologic conditions.

THE EFFECT OF ANXIETY ON INDUCTION OF ANAESTHESIA WITH PROPOFOL

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Background and aims:

Anxiety is thought to affect propofol requirements for bispectral index (BIS) suppression[1]. We investigated whether this is true for loss of verbal response, and

whether anxiety influences cardiovascular changes following propofol induction.

Methods:

We recruited 123 ASA I-II patients undergoing general anaesthesia into this prospective study. Preoperative state and trait anxiety scores were measured using the State Trait Anxiety Inventory (STAI). Propofol was administered at 40 mg.kg-1.hr-1. Propofol dose was recorded at loss of verbal response (PDLV) and again when BIS decreased to 50 (PDBIS50). Thereafter propofol infusion rate was reduced to 8 mg.kg-1.hr-1. Cardiovascular data were collected for fifteen minutes in total. Maximum percentage decreases in MAP (nadir MAP) and heart rate (nadir HR), and time to nadir MAP, were recorded. Airway obstruction was corrected if necessary.

Results:

Using multivariate analysis, anxiety scores were not significantly associated with PDLV, PDBIS50, nadir MAP, nadir heart rate or time to nadir MAP. Factors independently predictive of these endpoints were broadly consistent with previous studies. During propofol administration, black/black British ethnicity ($P = 0.045$), and increasing age ($P < 0.001$) and weight ($P = 0.003$), increased the risk of airway obstruction. BIS at loss of verbal response decreased with increasing propofol dose ($P = 0.026$) and was higher in white patients ($P = 0.023$) than in other ethnic groups.

Conclusions:

Anxiety, measured using STAI, has no effect on propofol dose requirements for induction or on associated cardiovascular changes.

[1] Maranets I, Kain ZN. *Anesth.Analg.* 1999; 89: 1346-51.

COMPARISON OF PATIENT MAINTAINED PROPOFOL SEDATION AND MIDAZOLAM BOLUS SEDATION FOR ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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Background and Aims:

Propofol target controlled infusion (TCI) devices can be modified, allowing patients to control their sedation. Comparing patient maintained propofol to midazolam sedation, this study evaluated sedation efficacy, safety and satisfaction during endoscopic retrograde cholangiopancreatography.

Methods:

60 patients were randomised into two groups. One group received midazolam at the endoscopist's discretion. The other group received 0.9µg/ml target propofol blood concentration initially. Pressing a handset, patients could increase this target by 0.2µg/ml increments, with a lockout interval of 2 minutes, to a 4.5µg/ml maximum. Cardio-respiratory data, sedation scores and interventions by the supervising anaesthetist were recorded. Questionnaires, completed by patients and endoscopists post procedure, were analysed with Mann – Whitney and Fisher's exact tests.

Results:

ERCP was completed in all cases without airway compromise. No statistically significant differences in monitored cardio-respiratory data were found. Median maximum target propofol level was 2.4µg/ml (range 1.4-4.1). Propofol recipients required more interventions ($p = 0.14$): six needed increased sedation; one had transient low saturation (91%). The median total midazolam dose was 3mg (range 2-5). One intervention for over sedation and one for hypotension occurred. The endoscopist's rating of cooperation and ease of the procedure was not significantly different between the groups. Patient satisfaction with propofol was higher ($p = 0.012$). Recall was higher with Midazolam ($p = 0.013$) with patients reporting more pain ($p < 0.0001$), nausea ($p = 0.0001$) and coughing ($p = 0.0002$).

Conclusions:

Safe patient maintained sedation was possible with propofol. In this model there were problems achieving adequate self-sedation. The patients who received propofol reported higher satisfaction and more amnesia.

PROPOFOL TARGET RATE IN MEDIUM AND ELEVATED MELD SCORE HCC PATIENTS

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TCI in HCC cirrhotic patients by PK-PD models is unreliable. Alterations caused by cirrhosis would mandate a correction of K10, made inadequate by HEB/neuronal alterations and renal failure. Cortical

activity lowers the longer TCI lasts and the lower MELD score is. This study aimed at recording target rates determining a CSIndex of 40 in HCC patients with different MELD scores undergoing hepatic resection and finding a Δ target compared with a control group. Materials & methods: Thirty patients were enrolled in group A (MELD 10-15), group B (MELD 15-20) and control group C. Exclusion criteria were MELD > 20 and temporary hepatic clamping. Propofol-Remifentanil TCI was performed by the Schneider-Minto model using Target View modality + Remifentanil 0.8-1 ng/ml for induction and Plasma Target modality for corrections. Results: Compared with controls, group B required Propofol concentrations of -33% at T0, successively decreasing to -25-26%. T test was statistically significant ($p < 0.00001$). Group A initially required a target concentration of -16%, the difference decreasing at T3-T4 ($p = 0.07$) to become significant again after 180'. Infusion rates differed significantly between groups A and B ($p < 0,00001$). A and B groups' awakening Target rates and decrement times were altered ($p < 0.001$). Conclusions: Trend graphics demonstrated a time-dependent decrease of propofol needs, with lower rates for group B. This might be explained by pharmacodynamic criteria or the inability of the kinetic model to compensate propofol increased context-sensitive half-life (fig.1). Propofol rates reduced by 25-30% are therefore recommended in MELD > 15 patients.

THE ANAESTHESIOLOGIST'S POINT OF VIEW IN THE SURGICAL TREATMENT OF MORBID OBESITY: TCI PROPOFOL & TIVA REMIFENTANIL ANAESTHESIA

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The anaesthetic management of massive and superobesity patients for weight-reducing surgery requires a good evaluation of the repercussions of pathological obesity on cardiovascular and respiratory function.

The operative risk is increased in obese patients due to technical difficulties, mainly during intubations, and to postoperative respiratory and thromboembolic complications.

The combination of general anaesthesia: TCI Propofol & TIVA Remifentanil and thoracic epidural, when it is possible, is an ideal technique for the anaesthetic management of these patients. It must be performed by specialized anaesthesia personnel in a specialized environment.

The objective of this management is to assess the operative risk, and to reduce it to an acceptable level by appropriate preoperative management taking into account the expected benefit of the surgical procedure.

Reference: Munsch Y, Sagnard P. The anesthetist's point of view in the surgical treatment of morbid obesity. *Ann Chir.* 1997;51(2):183-8

PROPOFOL AND REMIFENTANIL DRUG INTERACTION ON THE STATE ENTROPY OF THE EEG: SURFACE MODEL

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Nowadays general anaesthesia is guided using depth of anaesthesia monitors. These monitors convert information provided by the raw electroencephalogram (EEG) into an easy to understand index. The indices are used to aid the anaesthesiologist to evaluate the hypnotic state of a patient, and to decide upon the best drug combination so as to maintain the patient in a stable and safe state.

The objective of this work was to develop a model able to predict the hypnosis rate of a patient using only drug target concentrations. The depth of anaesthesia index used was the State Entropy of the EEG, which computes the Shannon entropy over the EEG (SE). Data recorded during 20 urological procedures, from patients under general anaesthesia (TIVA of propofol and remifentanil with TCI) were used to develop a drug interaction model. For each patient, the propofol and remifentanil effect-site concentrations combinations used were registered, and SE average and standard deviation values recorded. With this information, a 3D surface was adjusted to the propofol effect-site concentration, the remifentanil effect-site concentration, and Average SE (nonlinear least squares regression).

The model obtained was applied to the data sets, and performed adequately throughout the anaesthesia stages, following the real SE trend. The surface model obtained helps the anaesthetist to understand the behaviour of the drugs combinations and interaction. This model can be implemented in educational software, simulating SE values using a TCI of propofol and remifentanil.

Acknowledgements:

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REMIFENTANIL-PROPOFOL VERSUS DEXMEDETOMIDINE-PROPOFOL ANAESTHESIA FOR SUPRATENTORIAL CRANIOTOMY

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Background: The aims of the study were to compare the perioperative haemodynamics, propofol consumption and recovery profiles of remifentanil and dexmedetomidine when used with air-oxygen and propofol and to evaluate a postoperative analgesia strategy and undesirable side-effects.

Method: Group D patients (n=25), received i.v. dexmedetomidine 1 µg kg⁻¹ as preinduction over a 15-min. and 0.2-1µg kg⁻¹ h⁻¹ by continuous i.v. infusion during the operation period. Group R patients (n=25), received remifentanil 0.05 µg kg⁻¹ as induction i.v. over a 15-min period and 0.05-0.25 µg kg⁻¹ h⁻¹ as maintenance. The propofol infusion was started at a rate of 10 mg kg⁻¹ h⁻¹ and titrated to maintain BIS in the range 40–50.

Results:

Propofol doses for induction and maintenance of anaesthesia was lower with dexmedetomidine. The time for BIS to reach 50 was significantly shorter in Group D (p<0.01). When the groups were compared for the parameters of recovery; extubation time (p<0.01); response to verbal commands (p<0.05) and time for orientation (p<0.05) were longer with Group D. With respect to PACU discharge time, dexmedetomidine patients required a longer time in comparing remifentanil patients to achieve their first normal neurological score (33 min vs 31 min). The earliest opioid administration was at 38 min. in the dexmedetomidine group and 33 min. in the remifentanil group. Undesirable side-effects were similar in two Groups (Postoperative nausea and vomiting, shivering).

Conclusions:

Propofol-remifentanil and propofol-dexmedetomidine are both suitable for elective supratentorial craniotomy and provide similar intraoperative haemodynamic responses and postoperative adverse events.

PROCESS CONTROL IDENTIFICATION APPROACH APPLIED TO PROPOFOL PHARMACODYNAMIC MODELING

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In this work, we revisit PD modeling using an identification method used in process control. As compared to the traditional approach, process control identification accounts for the inertia (i.e., dynamics) of the monitor used to measure the effect. In addition, the order of the model is determined such that all linear dynamics are accounted for. Only then, a Hill non-linear function is calculated to further improve the fit.

Induction data following Propofol administration were obtained from 44 patients undergoing elective surgery. The drug effect on cortical activity was measured using the WAVCNS, an EEG-based index expressed in the familiar 100-0 scale, and whose dynamics with respect to a EEG change is modeled as a 2nd order linear function.

The identification results are presented in Table I. We found that Propofol PD can be modeled using a time constant kd and time delay Td (captures the arm-to-brain travel time). kd is significantly larger than the usual ke0 value, expressing a faster effect dynamics than anticipated in the literature. This result was expected since ke0 models both the physiological effect and the algorithmic inertia of the monitoring technology. We also report better fit, and less inter-patient variability.

TABLE I. Propofol Pharmacodynamic Models (Traditional and Process Control Approaches)

PATIENT #	TRADITIONAL PD APPROACH			PROPOSED PD APPROACH			
	LTI ke0 [s ⁻¹ ·10 ⁻³]	Hill EC50 [µg/ml]	γ	Td [s]	LTI kd [s ⁻¹ ·10 ⁻³]	EC50 [µg/ml]	Hill γ
G1: ≥18 - <30 years							
Mean	8.5	2.0	2.9	20.0	61.4	3.0	2.5
SD	3.8	0.7	0.6	13.9	40.1	0.6	0.8
G2: ≥30 - <40 years							
Mean	8.3	2.4	2.7	12.9	39.0	3.3	2.0
SD	3.8	0.6	0.7	12.6	19.0	0.4	0.4
G3: ≥40 - <50 years							
Mean	8.8	3.0	2.5	12.4	34.2	4.0	1.7
SD	3.8	1.2	0.4	9.1	3.1	1.0	0.3
G4: ≥50 - ≤60 years							
Mean	8.0	2.9	2.1	10.5	33.1	4.1	1.7
SD	3.1	0.7	0.6	8.8	11.8	0.7	0.4

Notes: Sample sizes: G1 (15), G2 (12), G3 (9), G4(8) ; SD: Standard Deviation

SUITABILITY OF CONSCIOUSNESS MONITORS FOR PD MODELING OF INTRAVENOUS ANESTHETIC DRUGS

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Since the advent of EEG-based monitors, pharmacodynamic PD models of intravenous anesthetics have been derived based on the output of such monitors in order to describe the relationship between changes in drug plasma concentration and changes in effect. However, very limited consideration is given as to their suitability for pharmacodynamic identification.

In this work, we check whether two such monitors, the BIS A-2000 (Aspect) and the NeuroSENSE NS-701 (CleveMed) are suitable, i.e., their dynamic behavior can be fully captured by a Linear Time Invariant (LTI) relationship across their whole output range. LTI models can be used to pre-determine the input profile needed to achieve a particular output.

Five EEG segments corresponding to different stationary cortical states were pieced together to form a number of EEG signals which were replayed simultaneously to both monitors. Their outputs were separated into training and validation data sets, and used to derive and test LTI models for each monitor, Fig. 1.

Our results show that the NS701 is reliably described by a linear model across its whole operating range. Conversely, no single linear model could yield good predictive performance for the A-2000, revealing the non-linear or time varying operation of its underlying algorithm.

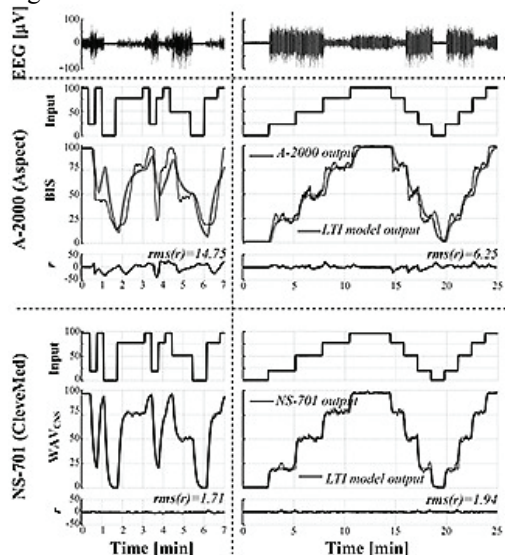


Fig. 1 Model identification and goodness of fit for two distinct data sets. Results show the poor predictive performance of the A-2000 model. In contrast, the NS-701 model describes accurately the behavior of the monitor. The difference in predictive performance is explained by fundamental differences in their algorithmic structure.

HIPPOCRATES TRAINER: PK/PD SIMULATOR, MONITORING AND CONTROL

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Background and aims:

Hippocrates is an advanced software simulation tool providing to the anaesthetist an instrument for training pharmacokinetic/pharmacodynamic (PK/PD) models. Hence, the module incorporates sophisticated generation of PH/PD models driven by simulated drug administration regimes. As the variability of the patient's responses is much wider than inferred by the PK/PD data available in the literature it is possible to use several drug model databases and enabling the user to generate new ones.

Methods:

The package incorporates a variety of control strategies for the control of neuromuscular blockade by continuous infusion of non-depolarising neuromuscular blocking drugs. This control simulation environment, provides robustness and adaptation to individual requirements, covering a wide and realistic range of situations. Furthermore, in addition to the noise reduction techniques and control strategies, there are some events that can be incorporated in the simulated patient through the graphic interface: measurement noise, faults or outliers, mismatch between real and measured weight, change in the individual PK/PD model parameters. The interface shows all relevant information, namely the bolus administration times and amounts, the current values for the infusion rate and T1%, the noise level and the patient database model number. The set point, the control strategy, the noise reduction technique, the simulation speed and the bolus amount can be selected and/or modified by the user through the toolbar in the graphic interface.

Results and Conclusions:

Hippocrates provides an excellent environment for education and training purposes. We expect that this package will encourage the clinical application of closed-loop drug infusion systems.

TCI PROPOFOL AND REMIFENTANIL ANAESTHESIA TITRATED WITH THE BIS-XP MONITOR

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Introduction:

BIS guided anaesthesia may reduce the incidence of anaesthetic "awareness" when muscle relaxants are used. Sub-anaesthetic concentrations of drugs inhibit memory formation and the possibility exists that patients having BIS guided anaesthesia may be conscious during surgery but without later recall. This study, using the Isolated Forearm Technique (IFT) was undertaken to investigate this problem.

Method:

20 women undergoing major gynaecological surgery had a low thoracic epidural inserted. Anaesthesia was induced using target controlled infusions (TCI) of propofol and remifentanyl and, during surgery, these drugs were titrated to maintain the BIS value in the range 55 – 60. Atracurium was used for muscle relaxation. When a patient responded to verbal command the TCI propofol was increased. Data from the BIS-XP (A 2000, Revision 3.3) was captured to a computer for later analysis. A positive BIS response was defined as an increase of 15 within 2 minutes before to 2 minutes after the IFT response.

Results:

13 women responded to commands during surgery and were thus conscious. The BIS detected 36 of the 66 IFT responses. Based on the prevalence of an IFT response, the BIS had a Positive Predictive Value of 0.17 for detecting consciousness during anaesthesia. One patient remembered something about "squeezing fingers".

Discussion & Conclusion:

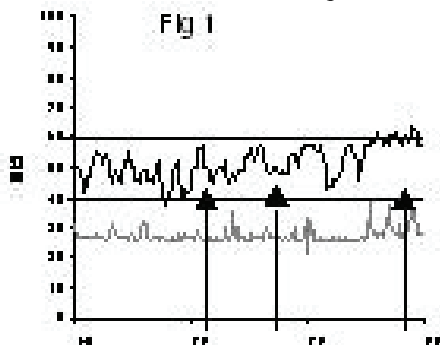
When using TCI propofol and remifentanyl with muscle relaxants, the BIS monitor cannot reliably predict consciousness during surgery.

Fig 1

BIS darker line

EMG lighter line

The 3 arrows indicate 3 IFT responses



REMIFENTANIL AND TIVA IN SPINE SURGERY

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Background and Aims: One hundred four patients (67 female, 37 male, average age 58,5 years old, average weight 77 kg; ASA I-II) was treated with spine stabilization L4-L5-S1 (238 min. average) using Total Intravenous Anaesthesia (T.I.V.A.) with Remifentanyl (R), Propofol (P) and Cis-Atracurium Besilato (CAB).

Methods: After having monitored vital parameters, we started anaesthesia with R infusion of 0,2 γ /kg/min. in the first 3 mins. then reduced to 0,15 γ /kg/min., P 2-2,5mg/kg and CAB 0,2mg/kg. R 0,15-0,10 γ /kg/min., P 6-8mg/kg/h and CAB 1,5 γ /kg/min insured maintenance of anaesthesia: we stopped CAB 45 mins. before the end of procedure. The starter dose of post-operative analgesia (Ketorolac 0,5 mg/kg + Tramadol 2 mg/kg + Alizapride 1 mg/kg i.v.) has been administrated at the beginning of sub-skin suture together with elastomeric pump (100 ml, 2ml/h) containing Ketorolac 150mg + Tramadol 600mg + Alizapride 250mg. R and P infusion was continued up to the suture of the skin. At the awakening we evaluated the sensory and motor activity of the inferior limbs with Prick Test and Bromage Score. After 1-4-8-12-24 hours from postoperative time we observed effects of analgesia through VAS score.

Results: 98% of patients had a prompt and soft awakening, only 2% complained PONV. After 4th hour only 7% of population had VAS score 5 and received a supplemental dose of Ketorolac 30 mg. Any side-effects or complications did not occurred during procedure.

Conclusions: R permitted haemodynamic stability and a reduction in intra operative blood losses and transfusion, which we have administrated only in 9% of subjects.

HIGH DOSE REMIFENTANIL INFUSION DOES NOT MAKE THE INCIDENCE OF PONV INCREASE

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Introduction:

It is reported that remifentanyl engenders very little nausea and vomiting because of its pharmacological characteristics, we examined the incidence rate of PONV among Japanese patients when larger and smaller

amounts of remifentanyl were administered, then compared their incidence with analgesia by fentanyl.

Subjects and Methods:

Subjects were 60 patients, 15–65 years old, who underwent normal operations of laparoscopic cholecystectomy. The subjects were separated randomly into three groups: 1) a high-dose remifentanyl group, dose amounts of remifentanyl in the induction time and in the maintenance time were 1 and 0.75 $\mu\text{g}/\text{kg}/\text{min}$, respectively; 2) a low-dose remifentanyl group, 0.5 and 0.25 $\mu\text{g}/\text{kg}/\text{min}$, respectively. 3) a fentanyl group, dose amounts of fentanyl in the induction time and in the maintenance time were 2 and 0.05 $\mu\text{g}/\text{kg}/\text{min}$, respectively. Regarding anesthesia, it was induced with propofol 4 $\mu\text{g}/\text{ml}$. As soon as pneumoperitoneum ended, the administration of propofol and opioids were also stopped. After bolus intravenous injection of fentanyl 2 $\mu\text{g}/\text{kg}$, PCA was connected. Measurement items were recorded for total amounts of remifentanyl, fentanyl, and propofol, the presence and degree of nausea and vomiting for 6–24 h after operation, and the total amount of fentanyl of postoperation PCA. [Results] With both high doses and low doses of remifentanyl, the incidence rate of PONV tended to be lower than in the fentanyl groups.

Conclusion:

Even if remifentanyl was used at a high dose is used during operation, the incident rate of PONV after operation was lower than that for fentanyl.

ADEQUACY OF THE TRADITIONAL PHARMACODYNAMIC APPROACH FOR MODELING INTRAVENOUS ANESTHETICS USING EEG-BASED QUANTIFIERS OF CORTICAL ACTIVITY

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Traditional PD modeling follows the approach pioneered by [1] aimed at modeling the dynamics observed between a change in plasma concentration and change in effect. This method is based on the derivation of a single rate constant ke_0 .

While this approach works well in many situations, we contend that the a priori model structure proposed by [1] is insufficient when deriving intravenous anesthetics PD

models based on an effect quantified by an EEG-based index.

For illustration, we show an example (Fig. 1) of an induction time course using propofol. The drug effect is quantified using the WAVCNS (v.1.2), an EEG-based index expressed in the familiar 100-0 scale.

To determine the adequacy of the identified model, we calculate the prediction error ep using the residuals and model parameters. The model adequately describes the identification data if ep has the characteristics of a white noise. This is verified by calculating its autocorrelation.

Clearly, ep is colored, i.e., all of the linear dynamics contained in the original data have not been accounted for. The model cannot be used reliably.

Similar results were obtained in an additional 43 inductions. We conclude that the a priori structure of traditional PD models is inadequate.

[1] Sheiner..., Clinical Pharmacology Therapeutics, vol(25), 1979.

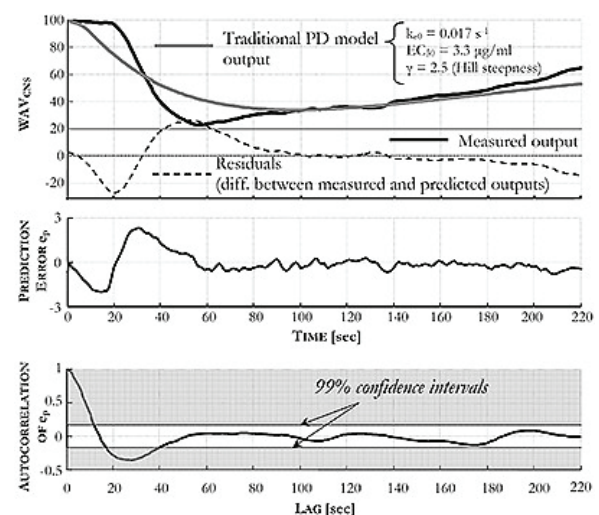


Fig. 1 PD identification results using the traditional approach and based on a propofol induction time course.

REMIFENTANIL VERSUS SUFENTANIL FOR VIDEOLAPAROSCOPIC SURGERIES UNDER TOTAL INTRAVENOUS ANESTHESIA: A COMPARATIVE STUDY

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Introduction: Total intravenous anesthesia (TIVA) is most commonly performed with remifentanil associated to target controlled infusion (TCI) of propofol. The purpose of this study was to compare two TIVA drug

schemes for videolaparoscopic surgeries: propofol TCI associated with continuous infusion (CI) of remifentanyl or sufentanyl. Method: Sixty ASA I-II adult patients of both genders were randomly assigned to two groups according to the opioid infusion to be employed: GR patients were given 0.3 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ remifentanyl CI for induction, while GS patients received 0.5 $\mu\text{g.kg}^{-1}$ sufentanyl bolus followed by 0.5 $\mu\text{g.kg}^{-1}.\text{h}^{-1}$ CI. Propofol TCI (4 $\mu\text{g.ml}^{-1}$) was installed in both groups 3 min. after starting opioids CI, and was adjusted to keep BIS within 40-50 range during maintenance. Opioid infusions were interrupted at the end of procedure in GR and 20 min. before that in GS. For postoperative pain control, all patients were given 1.5 mg.kg^{-1} ketoprofen and 30 mg.kg^{-1} dipirone 30 min. before surgery completion; tramadol 100mg was used in PACU if needed.

Results: There were no statistical significant differences between groups regarding anesthesia duration, propofol dose, time to waking up and mean HR. Mean MAP was higher in GS (91,9 vs 77.6 mmHg, $p < 0,0001$), while GR patients stayed longer in PACU (76 vs 49 min, $p < 0,0001$). Pain complaints were more frequent in GR (22 vs 1 patient, $p < 0,0001$), as did PONV (10 vs 2 patients, $p = 0,009$).

Conclusions: TIVA with sufentanyl showed better circulatory stability. Remifentanyl patients presented more pain and PONV in PACU, what made them remain longer there.

REMIFENTANIL IN PEDIATRIC SURGERY

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Background and aims: Thirty-six patients (18 female, 18 male; average age 15 months; average weight 8 kg; ASA I-II) with VesicoUreteral Reflux (RVU) were treated with surgery (110 mins. average) using Balanced General Anesthesia.

Methods:

Induction of anesthesia was performed with a mixture of O₂/Air and Sevoflurane (4-6%). After having established venous access, patients were premedicated with Atropine 0,1 mg i.v. After that Propofol (2 mg/kg) and Atracurium besilate (0,5 mg/kg) were administered. IOT was performed, continuous infusion with peristaltic pump of Remifentanyl (R) (25 γ/ml ; 0,30 $\gamma/\text{kg}/\text{min}$) was started for 5mins. Anesthesia was maintained with Sevoflurane (1,5-2%) and R (0,15-0,20 $\gamma/\text{kg}/\text{min}$). At skin suture Tramadol (2 m/kg) + Ketorolac (0,5 mg/kg) + Alizapride (1 mg/kg) i.v. were given and R was ended.

ECG, HR, NIBP, SaO₂, EtCO₂ were monitored every 5 mins. Analgesic level was evaluated with the aid of Objective Pain Scale (OPS) at awakening.

Results:

A satisfactory anesthetic-analgesic level was reached after 3 mins. It was maintained during all surgery procedure, in order to allow a reduction of Sevoflurane concentration by 0,5 %. No alterations of vital parameters was observed. The awakening was prompt and soft in all patients. After awakening in 89% of patients OPS was ≤ 4 , in 11% instead OPS was 6 and required an additional dose of Tramadol (1 mg/kg) i.v.

Conclusions:

The present anaesthetic-analgesic protocol allowed for better compliance and optimization of analgesic level during middle-long surgery in pediatric patients. No complications (thoracic rigidity, bronchospasm) were observed.

CONTRIBUTIONS TO THE CONTROL OF INTRAVENOUS DRUGS: REDUCED COMPLEXITY MULTIVARIABLE PREDICTIVE ADAPTIVE CONTROLLER

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The problem of controlling the level of unconsciousness measured by the Bispectral Index of the EEG (BIS) of patients under anaesthesia, is considered. The manipulated variables are the infusion rates of the hypnotic drug propofol and analgesic drug remifentanyl. In order to tackle the high uncertain present on the system, the predictive adaptive controller MUSMAR is used. The performance of the controller is illustrated by means of simulation with 45 patient individual adjusted models (nonlinear models), which incorporate the effect of the drugs interaction on BIS. This work presents a feasibility study of the control of the BIS exploring the above ideas. Simulations performed on a nonlinear model relating BIS with the doses of propofol and remifentanyl yield results complying with the specifications. These results show that such a control structure could be adequate to control the BIS signal during total intravenous anaesthesia. Furthermore, for a clinical implementation of the controller an empirical system needs to be incorporated, so as to supervise the online adaptation of the parameters. A key feature in the control of anaesthesia is to achieve a good rejection of disturbances caused by interfering actions from various

sources. The practitioner is therefore able to anticipate some induced disturbances, acting to counteract them even before their effects are visible. A major challenge for the automation of anaesthesia consists in replicating similar performances. Clearly, this calls for the use of feedforward from measurable signals correlated with disturbances (e.g. EMG).

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IMPROVING THE ASSESSMENT OF INTERINDIVIDUAL VARIABILITY IN ANAESTHESIA PRACTICE THROUGH A HYBRID METHOD

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Background and Aims: The aim of this work is to introduce novel and improved results in the assessment of interindividual variability in anaesthetic practice.

Methods: These improvements are achieved by first estimating the individual patient PK/PD parameters through a hybrid method which outperforms the usual methods of parameter estimation. This in turn leads to better results in the prediction of the individual response to anaesthetics drugs. Therefore, the proposed approach is useful for individual patient description, simulation and control purposes. The hybrid method here considered consists in combining an artificial neural network with a suitable curve fitting algorithm: the network produces the initial parameter estimate based on some data collected from the patient and then, if necessary, the fitting algorithm refines on-line this estimate.

Results and Conclusions: We illustrate our technique using neuromuscular blockade data collected from patients that undergone general anaesthesia at Hospital Geral de Santo Antonio. In the considered cases one of two drugs were used: mivacurium and atracurium. The results are compared to those that are obtained using a classical curve fitting algorithm, and proved to present a much better performance.

CONSCIOUS SEDATION WITH REMIFENTANIL DURING LOCO-REGIONAL ANAESTHESIA

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Background and Aims: Alterations of the emotional state due to pain represent an important problem that needs prompt resolution to avoid further “psychological trauma” to patients. Method of exclusion are obese subjects (body weight >100 kg) with allergic diathesis and BPCO asthmalike.

Methods: We examined one hundred patients (57 female, 43 male; average age 47 years old; average weight 63,2 kg; ASA I-II) undertaken to upper orthopaedic surgery (63mins. average) using Peripheral Loco-Regional Anaesthesia. The population was premedicated with Alizapride 50 mg + Midazolam 0,03 mg/kg i.v. Soon after continuous infusion of Remifentanil (R) 0,04 μ g/kg/min. was started. Ten minutes later, the peripheral block (PB) was performed. R infusion was maintained until the end of operation. Every 5 mins the degree patient anxiety was evaluated with the aid of Sedation-Agitation Scale (SAS). ECG, HR, NIBP, SaO₂ at the same interval were measured.

Results: Prior to start surgery, SAS was 6 (very agitated) in 60% of the patients and 5 (agitated) in 40% of the patients. During surgery SAS was 4 (calm and cooperative) in 80% of the patients and 3 (sedated) in 20% of subjects. At the end of operation SAS was 4 in all the patients. Bronchospasm with thoracic rigidity occurred in 5% of the patients and it was resolved with pharmacological therapy. PONV was not observed in any patients.

Conclusions: From the clinical experience R reduced anxiety and discomfort of the patients demonstrating a minor percentage of complications without alterations of vital parameters.

ANALGOSEDATION AND AWAKE CRANIOTOMY: TWO DIFFERENT ANESTHESIOLOGIC TECHNIQUES TO GUARANTEE PATIENT COOPERATION AND CEREBRAL HOMEOSTASIS

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Background and aims: There is an increasing trend towards performing awake craniotomy. The challenge for the anaesthesiologist is to provide adequate analgesia and sedation, haemodynamic stability and a safe airway with an awake cooperative patient for neurological testing.

Methods:

Not all patients need the same awake condition during craniotomy. When the speech area is involved, we need a cooperative and awake patient, able to speak; on the other hand, when only motor and sensitive areas are involved it is mandatory to control the movements of depending structures. We have performed two different intravenous anaesthetic techniques with propofol and remifentanyl in 12 patients (7 with speech area involved, 5 with just motor or sensitive area involved). In the first group (A) the patients were just sedated with low doses of propofol (TCI, 1.5 µg/ml) and remifentanyl (TCI 1-2 ng/ml) and maintained; in the second one (B) the patient is sedated and intubated with low doses of propofol (TCI, 1.5 µg/ml) and remifentanyl (TCI 2-4 ng/ml). We analysed p_aCO₂ and ETCO₂ in all patients. We noted the quality of anaesthesia, analgesia and quality of recovery and the complications of each group.

Results:

We analysed 12 procedures. Group B had the fewest complications. No patients in this group developed hypercapnia compared with patients of group A. No patients in group B required additional analgesia compared with patients of group A.

Conclusions:

We have developed a double technique for craniotomy which facilitates awake neurological testing. Both the techniques are safe and obtain good patient satisfaction. In the group B we guarantee also the best ventilation pattern obtaining the best conditions to guarantee cerebral homeostasis.

TOTAL INTRAVENOUS ANAESTHESIA FOR GROSS OBESITY PATIENTS

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Introduction:

The number of obese patients undergoing anesthesia and surgery is increasing.

Methods:

This study aims to present recent our achievements in the management of 460 gross and morbidly obese patients in order to improve safety.

Results:

Our current investigations of 460 obesity patients undergoing for elective laparoscopic surgeries have demonstrated that the type of anesthesia (total

intravenous anesthesia: TIVA, TCI or volatile: sevoflurane, desflurane) and the anesthetics (propofol lipuro, remifentanyl and NMBA; cisatracurium, rocuronium) used have an important influence on the perioperative period, especially on postanesthesia recovery and respiratory failure during the postoperative period. These findings were compared with previous our results and publications. Practical advice is also presented for performing successful intubation and mechanical ventilation in the morbidly obese patient, as well as describing drug dosage and administration.

Conclusions: The progress in anesthesia techniques and modern drugs allows for safe management of obese patients, with mortality decreasing in this group of patients.

A LEARNING REGRESSION MODEL FOR DISCRIMINATION OF HEMOGLOBIN-EFFECTS ON AJVDO₂

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Background:

Arterial-jugular bulb difference of oxygen content (AJVDO₂) can be related to cerebral blood flow and oxygen consumption. Plasma hemoglobin concentration (Hb) has been reported to have two-edged effect on AJVDO₂. Hb increases oxygen contents of both arteries and jugular bulb, and net effect is reduction of AJVDO₂. Hb increases blood viscosity, and could raise AJVDO₂, conversely. This study was designed to discriminate the Hb-effects on AJVDO₂ mathematically.

Methods:

Sixty healthy adults were enrolled in this study. General anesthesia and mechanical ventilation were conducted. Arterial and jugular bulb catheters were located. At first, normocapnic state was achieved and defined as PaCO₂ = 38.9 +/- 1.9 mmHg, and hypocapnic state defined as PaCO₂ = 30.3 +/- 2.5 mmHg. Longitudinal data including 1/AJVDO₂, PaCO₂, Hb, mean arterial pressure (MAP), temperature (T) and anesthetic concentration (EC) was recorded at each state. Various regression models were applied to fit 1/AJVDO₂ and several dependent variables described above. Final regression equation was selected using loglikelihood ratio and analysis of residuals.

Results:

1/AJVDO₂ was well regressed by PaCO₂ and Hb. Equation was $1/AJVDO_2 = 0.0903 - 0.0263 \times Hb + 0.0011 \times PaCO_2$ (nested in Hb). Statistical significance was 0.00 and r² was 0.60. Median (interquartile ranges) of residuals was calculated at -0.005465 (-0.03772 ~ 0.03615).

Conclusions: Our equation has a good understanding with classical concepts on two-edged effect of hemoglobin. Rheologic effect of hemoglobin is dominant in our study design and hemoglobin lowers 1/AJVDO₂ in itself. PaCO₂ raises 1/AJVDO₂ at a constant level of hemoglobin.

TCI FOR SEDATION IN RHINOLARYNGOSCOPIC AMBULATORY SURGERY

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Object: Ambulatory surgery has raised during last years. In our hospital interventions for nasal and vocal cord lesions are performed in local anaesthesia and a conscious sedation that enables the cooperation of the patients. We evaluate the effectiveness and safety of the target-controlled infusion (TCI) system during rhinolaryngoscopic surgery. Methods: We enrolled 22 patients (ASA 1 and 2), that were randomly assigned to one of the three following groups. The group A received only propofol with the Schnider pharmacokinetic model in effect site control. The starting target concentration was 1 mcg/mL. Then we increased the Ct of 0,2 mcg/mL to obtain an effective sedation (Ramsay scale value of 2 or 3). In the group B a bolus of fentanyl (0,5-1 mcg/kg) was administered in association with TCI propofol. In the group C patients used TCI system with propofol and remifentanyl (Minto model). Patients breathed spontaneously and cooperated during the operation.

Results: The median Ct propofol was 2 mcg/mL in the group A, 1,7 mcg/mL in the group B, 1,55 mcg/mL in the group C. The median plasma Ct remifentanyl was 0,9 ng/mL. The median induction time was 7,5 minutes while the median operation time was 30 minutes. There were no statistical difference in the three groups. There were no episodes of hemodynamic instability, apnoea or oxygen desaturation. Conclusions: TCI propofol sedation, alone or in association with fentanyl or TCI remifentanyl, is a safe and effective anaesthetic technique that allow a fast dimission to home.

PERFORMANCE CHARACTERISTICS OF THREE TCI DEVICES IMPLEMENTING THE MARSH MODEL

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Background: There are several commercially available propofol target-controlled infusion (TCI) devices and pharmacokinetic simulation software packages. We compared the output of different simulation programs with each other, and with the output of TCI devices.

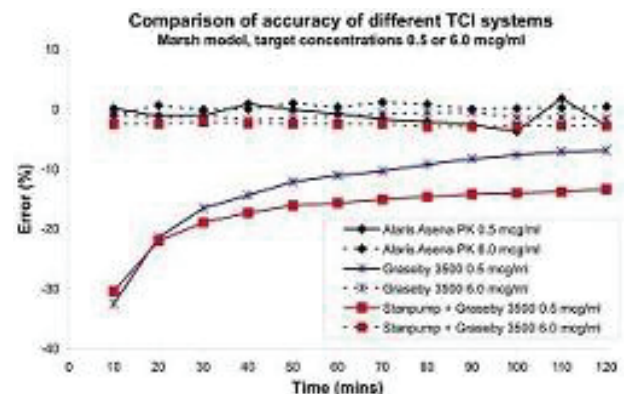
Methods: We used Stanpump, TIVATrainer and Rugloop to calculate the volumes required to achieve target propofol concentrations of 0.5 and 6.0 mcg/ml for 120 minutes. Thereafter 3 infusion devices were used to administer 1% propofol by TCI (both target concentrations for 120 minutes) into a measuring flask placed on a high precision scale. The volume of propofol delivered was calculated from the measured mass.

Devices Used Were: (1) Alaris Asena PK pump; (2) Graseby 3500 pump; (3) PC running Stanpump software controlling a Graseby 3500 pump. The Marsh model was used for each simulation and infusion device. Experiments were conducted under identical conditions; the flask was sealed to avoid evaporation during the experiment.

Results: Simulation programs: The propofol volumes calculated by the different programs were almost identical.

Infusion devices: The infusion devices implemented infusion regimens very similar to those calculated by simulation programs. Accuracy of the Asena pump was generally within 2%. The Graseby infusion pump overestimated the infused volume by upto 30% when used at a target of 0.5mcg/ml.

Conclusion: When used at low infusion rates, either as a standalone TCI device, or under the control of external software, the Graseby 3500 infusion pump significantly overestimates the volume of propofol it administers.



TCI FOR MULTIPLE DRUGS: THE TWO DIMENSIONAL USER INTERFACE APPROACH

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Background: No integrated platform has emerged that supports TCI dosing of several drugs. Separate TCI pumps for propofol and remifentanyl or alfentanil cannot account for the 15%-reduced remifentanyl/alfentanil elimination caused by propofol [1,2].

Methods:

These requirements were defined for a combined TCI system: 1) interacting pharmacokinetics are considered for model calculation of TCI dosing profiles, 2) drug dosing can be changed for all pumps through a single point of interaction, 3) dosing is based on a relevant endpoint for anesthesia (effect steering), 4) changing the hypnotic/opioid concentration ratio shall not unintentionally change depth of anesthesia. A prototype was built using MATLAB to verify results in simulations.

Results: To fulfill the requirements a two-dimensional (2D) drug display was designed. Isoboles representing the probability to tolerate a noxious stimulus are drawn in a 2D interaction map with the effect concentrations of the hypnotic and opioid as axes [3]. To set a target effect a point is selected within the 2D interaction map, identifying distinct hypnotic and opioid effect concentrations. The pumps are then steered in an interlocked way considering interacting pharmacokinetics to 1) reach the new effect (isobole) as fast as possible and then 2) to attain the selected hypnotic/opioid ratio moving along the isobole. The prototype provided evidence for the validity of the concept and also enforced the benefit of a 2D drug display.

Conclusions: A 2D drug display provides a transparent and powerful user interface for multiple drugs TCI systems.

References:

- [1] *Anesthesiology* 2002;97(6):1350-62.
- [2] *Anesthesiology* 2001;94(6):949-57.
- [3] *Anesthesiology* 2004;101:A504.

AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCKADE: A PILOT CLINICAL STUDY

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Background and Aims: This work reports a pilot clinical study of a system (software package Hippocrates) for the automatic control of neuromuscular blockade by continuous infusion of non-depolarising neuromuscular blocking drugs. A study (60 patients) was approved by the Ethics Committee of the Hospital Geral de Santo António in order to assess and to compare the performance of the different control strategies: fixed-parameter digital PID, on-line autocalibrated PID and multiple model switching PID.

Methods: The control module is easy to set up in clinical environment. It consists of a Datex AS/5 NMT sensor, a delivery pump and a portable computer. After the set up is completed, Hippocrates can be initiated and a sequence of interface menus drive the user to the execution of several tasks: initialization of the serial port settings and sampling time, initialization of the patient file including personal data such as name, weight, height, age and sex along with some specific surgery and anaesthesia information and definition of the filtering and control strategy.

Results and Conclusions: During the period of automatic control, the results for all patients were clinical satisfactory, with a good reference tracking in the great majority of them. A detailed comparison of the performance of these control approaches is described. The clinical experience obtained with Hippocrates along with the robustness of the control algorithms implemented points to the regular use of this system in clinical practice.

ASSOCIATION OF LMA AND TIVA IN AN INFANT WITH MILIARY TUBERCULOSIS

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Introduction: A 5-month-old infant (4.8 kg body weight) presenting with a severe picture of miliary pulmonary tuberculosis associated with a tbc meningitis underwent 2 distinct procedures: a ventriculostomy and a central line placement. The baby was very unstable, having a low to moderate oxygen need and a poor neurological status. Settings were both the operating room and the intensive care unit.

Methods: The procedures were performed under total intravenous anesthesia (TIVA) using S-ketamine and propofol. Airway was secured using a laryngeal mask airway (1.5 LMA, Rusch, Germany). S-ketamine (1 and 1.5 mg/kg i.v. for central line placement and ventriculostomy, respectively) was administered first, then propofol infusion was started at 10 to 15 mg/kg/hr whereas a bolus dose of 4 mg/kg was given immediately before LMA insertion. Anaesthesia was maintained with propofol 10-30 mg/kg/hr under continuous noninvasive monitoring (HR, SpO₂, EtCO₂, NiBP). Long-lasting local anesthesia (0.2% ropivacaine) was utilized in both procedures; postoperative pain control only required rectal codeine-acetaminophen association.

Results: Both procedures were carried out successfully, without cardiorespiratory derangements. No significant hypotension occurred. Emergence was uneventful with absence of agitation and stable respiratory drive. No vomiting or significant complications were recorded in the post-anesthesia period.

Discussion: LMA was preferred to avoid further pulmonary injury and to minimize the risk of transmission/inquination through the anesthesia breathing circuit. Moreover, TIVA instead of halogenated agents was deemed safer for liver function in the presence of a multidrug antitubercular chemotherapy. Propofol/ketamine association allowed the maintenance of an adequate level of anaesthesia with prompt awakening.

ANESTHESIA FOR RADIATION THERAPY IN PEDIATRIC ONCOLOGY - REVIEW OF 3850 CASES

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Background and Aims:

In recent years, propofol has become widely used for radiation therapy in children due to its rapid and predictable induction of anesthesia and easily titratable depth, maintenance of spontaneous ventilation with minimal need for airway manipulation and rapid recovery.

Methods:

We retrospectively evaluated total intravenous anesthesia-related complications during pediatric radiation therapy over 24 months.

Results:

One hundred and seventy-seven patients received a total of 3850 radiation interventions under propofol-based anesthesia (3833) or sedation (17). The average number of procedures per patient was 21.7. (median 27, range 1-74). The median age at the beginning of the treatment was 3.6 years (range 0.4 to 21.6); age distribution was: 2 yrs (38, 21.5%), between 2 and 4 yrs (60, 33.9%), and >4 yrs (79, 44.6%). The most common diagnosis was brain tumor (102, 57.6%). There were 3611 radiation sessions and 222 simulations. Forty-nine complications were identified (1.28%): 46 airway-related complications and 3 hemodynamic status changes. There were no episodes of laryngospasm and no patients required endotracheal intubation. Risk factors for the development of complications determined by univariate analyses were: addition of benzodiazepines, opioids or ketamine to propofol, length of anesthetic, total propofol dose (mg/kg) and simulation treatment. We found no evidence for the development of tolerance to propofol.

Conclusion:

Our overall complication rate of 1.28% was lower than that observed in comparable studies. Risk factors were total propofol dose (mg/kg), use of adjuncts, length of anesthetic and simulations.

SUITABILITY OF INDUCTION DATA TO CHARACTERIZE THE STATIC DRUG VS. RESPONSE RELATIONSHIP OF INTRAVENOUS DRUGS

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Static dose/response (SDR) relationships quantify the drug effect (i.e., response) resulting from a given drug dosage. The preferred approach to determine SDRs is to use a TCI system to progressively increase or decrease the plasma concentration in a step-wise fashion, each step providing a single point on the SDR characteristic.

We have developed a method for the identification of PD models for intravenous drugs using a process control identification approach. The advantage of our method is that it ensures that all of the linear dynamics are captured in the model. In case of a rapidly changing effect (e.g., induction), our approach removes all of the linear dynamics, leaving only information that cannot be explained by the linear model. This information can, in turn, be used for the identification of the non-linear SDR.

We derived the SDR curve using 44 propofol induction time courses. We compared our results to that of [1], who used the standard TCI approach described above. Our results are summarized in Fig. 1 and show a remarkable agreement with [1].

We conclude that induction data can be used to derive SDRs, which has the advantage of requiring only short and easily obtainable data, without requiring TCIs.

[1] Kazama..., *Anesthesiology*, vol(90), 1999.

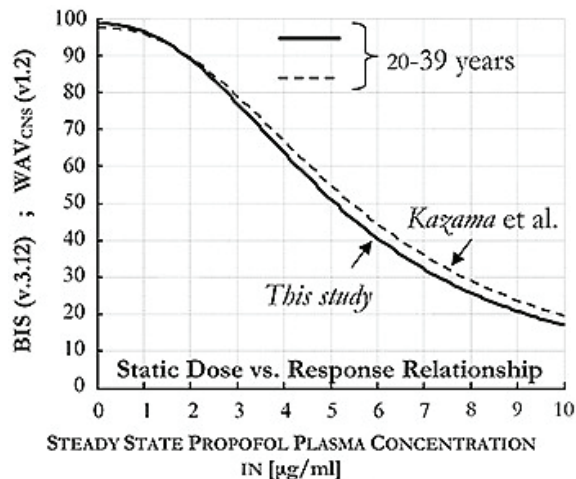


Fig.1 Comparison of the propofol SDR obtained by [1] using the BIS (v.3.12), and the SDR obtained in the present study using the WAV_{CNS} (v.1.2). The SDR derived in this study was based on data obtained from induction time courses. Each time course lasted in average between 2 and 3 minutes.

HEADSPACE MEASUREMENTS OF PROPOFOL ABOVE BLOOD SAMPLES BY ION-MOLECULE-REACTION MASS SPECTROMETRY

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Background: Propofol is an aromatic compound with low water solubility and low vapor pressure (0.142 mmHg at 20°C). These properties allow diffusion of propofol into the airspace immediately above propofol containing blood samples. The aim of this study was to test the hypothesis that headspace measurements of propofol by IMR-MS can replace the biochemical determination of propofol blood levels which are cumbersome to measure and generally unavailable during total intravenous anesthesia (TIVA).

Methods: Blood samples were drawn from 6 patients during TIVA using a target controlled infusion (TCI) device. For detection of volatile propofol, a gas analyzer based on ion-molecule-reactions coupled with quadrupole-mass-spectrometry (IMR-MS) (1) was connected to an auto-sampling device which allows automated gas sampling in the headspace immediately above liquids without direct contact with the solution. Propofol whole blood levels were determined by conventional liquid chromatography tandem mass spectrometry and served as a gold standard against which headspace measurements were compared.

Results: Propofol could be detected in the headspace above all blood samples. Pearson's correlation coefficients between headspace and whole blood propofol measurements in individual patients were highly significant ($p < 0.001$) and ranged from $r^2 = 0.72$ to $r^2 = 0.92$.

Conclusions: There is a linear relationship between propofol concentrations within a blood sample and levels of volatile propofol measured immediately above the sample. The rapid determination of headspace propofol could allow the on-site calibration of TCI devices and thus considerably improve the precision of target controlled propofol administration.

Acknowledgements:

Airsense Mass Spectrometry Systems, V&F medical development GmbH (1), Absam, Austria

TARGET CONTROLLED INFUSION OF ROCURONIUM: PHARMACODYNAMIC EFFECTS OF THE WIERDA MODEL

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This study was undertaken to evaluate the pharmacodynamic (PD) effects of the Wierda model of rocuronium administered by the TCI system.

Methods: 20 adult patients of ASA class I-III undergoing ENT surgery were premedicated with midazolam 1-2 mg. Anaesthesia was induced with propofol infusion at Cp of 4 mcg/ml and maintained with propofol TCI at 2-3 mcg/ml, remifentanyl TCI at 2.5-5.0 mcg/ml and BIS index between 40-60. Rocuronium was started in TCI according to the pharmacokinetic (PK) of the Wierda model to produce within 30 sec a theoretical Cp of 8 µg/ml with an infusion pump connected to a laptop run by a STANPUMP software and then tapered off. The neuromuscular function was monitored by the TOF-Watch-SX acceleromyograph. Spontaneous recovery

was observed up to a T4/T1 ratio of 0.9 after which all patients were extubated.

Results: We studied 12 females and 8 males. Mean age was 41.8(SD ±19.4) year , weight was 64.6(SD±11.0) Kg, height 167.3(SD±10.3) cm , bolus dose 0.38 mg/Kg, clinical duration 17.2(SD±2.2) min, EC50 1.13(SD±0.27) mcg /ml.

Discussion: The clinical duration reflects the bolus dose and is a consequence of the Vc that is 45 ml/kg in the Wierda model, very different from others PK models of rocuronium described by different authors. The EC50 of 1.13 mcg/ml, was comparable to the 0.95 mcg/ml reported by Saldien et al. Even if more PK and PD studies will be useful in the future, up to now the Wierda model seems to be reliable for the TCI use.

TOTAL INTRAVENOUS ANAESTHESIA VERSUS DESFLURANE ANAESTHESIA MAINTAINED FOR ARTHROSCOPY OF THE KNEE

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The aim of this study was to compare desflurane based anaesthetic maintenance versus total intravenous anaesthesia (TIVA) for arthroscopy of the knee.

Patients and Methods: After obtaining approval from local ethics committee, we studied 40 patients ASA physical status I-II, age 20-55 years undergoing arthroscopy of the knee under general anesthesia.

General anesthesia was induced with fentanyl 1 µg/kg and thiopental 5 mg/kg IV in desflurane group (n=20), or remifentanyl 1 µg/kg and propofol 2 mg/kg IV in TIVA group (n=20). Anesthesia was maintained with propofol 9 mg/kg/h and 0.25 µg/kg/min remifentanyl in TIVA group; desflurane (4-6%) and 66% N₂O in oxygen in desflurane group. Side effects of the drugs which were used during the operation were recorded. Postoperative Aldrete and DMRT scores were recorded. Also cost-effectivity of both groups were evaluated.

Results:

Intraoperative hemodynamic and BIS values of TIVA group were significantly lower when compared with the basal values of TIVA and desflurane group (p<0.05). After surgery, patients' extubation, eye opening, and orientation time were also significantly shorter in the desflurane group than in the Propofol group (p<0.05). In TIVA group patients needed analgesics rather early than desflurane group. In early postoperative period Aldrete and DMRT scores of the groups were similar. The cost-effectiveness of desflurane group was significantly lower than TIVA group.

Conclusion:

Desflurane anesthesia may be preferred to total intravenous anaesthesia because of its early recovery and cost effectiveness in outpatients knee-arthroscopy.

Key Words: TIVA, desflurane, outpatient anaesthesia, cost, emergence recovery characteristic.

HOW TO CORRECT MINTO'S PHARMACOKINETIC SET IN MORBIDLY OBESE PATIENTS: THE "FICTITIOUS HEIGHT" IN WOMEN (I)

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Background: There are some concerns regarding weight input for remifentanyl TCI in morbidly obese patients, since Lean Body Mass (LBM), which turned out to be a significant covariate for central and rapid peripheral compartments, and also for metabolic clearance, is defined by equations that have an odd property.

Methods: Since for this model the significant covariate is LBM only (not weight and height incorporated separately), it is possible to use a "fictitious height" in order to have the right LBM value calculated and used for the pharmacokinetic model-driven infusion while using the patient's total body weight as input weight. This way, the calculated LBM value corresponds to the value that would be obtained with a DXA scan in the same individual.

Results: The equation was derived with a simple mathematical process and is shown in Figure 1.

Conclusions: This equations corrects Minto's pharmacokinetic set in morbidly obese female patients.

$$h_{Fict} (women) = \sqrt{\frac{148 \times TBW \times (8.78 \times 1}{124.6 + 1.07 \times \dots}}$$

Figure 1: how to calculate the fictitious height (h_{Fict}) in women. TE and LBM for body mass index

GREATER PERIPHERAL BLOOD FLOW BUT LESS BLEEDING WITH PROPOFOL VS SEVOFLURANE DURING SPINE SURGERY

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Background: Despite the general acceptance of controlled hypotension as effective in reducing blood loss during spine surgery, the changes of blood flow that occur to the lumbar paraspinal muscles during hypotension remain unclear.

The aim of this prospective, randomized, single blind study was to compare the effects of sevoflurane and propofol on the lumbar paraspinal muscles regional blood flow when controlled hypotension was used during the surgery.

Methods: Blood flow of the lumbar paraspinal muscles was assessed by means of a laser Doppler flowmeter

during the prehypotensive and hypotensive (defined as a 30% reduction of baseline mean arterial pressure) period in 32 patients undergoing lumbar spine surgery. Patients were randomized to receive either sevoflurane or propofol as main anaesthetic agent to achieve hypotension. A continuous remifentanyl infusion was used for intraoperative analgesia. At the end of the surgery, blood loss and intraoperative bleeding (VAS ranging from 0 to 100) were evaluated by the surgeon.

Results: Peripheral blood flow was significantly greater in the propofol group both before and during the hypotensive period (median values of 22.2 FU vs 8.6 and 23.2 FU vs 9, respectively). Despite this fact, blood loss and intraoperative bleeding were significantly reduced when propofol had been used ($p < 0.01$).

Conclusions: Despite the greater blood flow, propofol causes less bleeding than sevoflurane during spine surgery and could be considered the anaesthetic of choice.

ROLE OF TOTAL INTRAVENOUS ANAESTHESIA ON ISCHAEMIC PRECONDITIONING IN PATIENTS UNDERGOING LIVER RESECTION

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Introduction:

It has been shown that brief ischaemic episodes, followed by periods of reperfusion, increase the resistance to further ischaemic damage. This response is called ischaemic preconditioning (IP). Stimuli other than ischaemia, such as hypoxic perfusion, tachycardia and pharmacological agents have preconditioning-like effects. Several animal studies demonstrate that volatile anesthetics offer more protection against ischemia-reperfusion injury than intravenous anesthetics. The aim of this prospective randomised double-blind study was to compare the effect of intravenous (TIVA) and inhalational (IA) anaesthesia on IP in patients undergoing liver resection.

Methods:

40 patients, aged 18-75, ASA I-III undergoing liver resection were enrolled. IP was used in all the patients. Induction of anaesthesia was standardized. For the maintenance, patients were randomized in two groups: TIVA and IA in which propofol TCI (4-5 mcg/Kg) and desflurane (1-1.5 MAC) were respectively used. The following dependent variables were considered: aspartate aminotransferase (AST), alanine

aminotransferase (ALT), total bilirubin, cholesterol, prothrombin time. They were measured before surgery and after 24, 72 hours and 7 postoperative days. Anova was used for statistical analysis.

Results:

There were not significant differences in the variables studied between the two groups.

Conclusions:

Volatile anesthetics do not offer more protection against ischemia-reperfusion injury than intravenous anesthetics during liver resection performed with IP.

References:

1. Nuzzo G, Giuliant F, Vellone M, De Cosmo G et al. Pedicle clamping with ischemic preconditioning in liver resection. *Liver Transpl* 2004;10:S53-7.
2. Hawaleshka A, Jacobsohn E. Ischaemic preconditioning: mechanisms and potential clinical applications. *Can J Anaesth* 1998;45:670-82.

INTRAVENOUS KETAMINE AND MIDAZOLAM FOR SHORT PEDIATRIC SURGICAL INTERVENTIONS

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Background and Aim: Ketamine is a unique drug giving complete anesthesia, analgesia and amnesia. In this study we present our 17 year experience performed with ketamine, midazolam and fentanyl. The aim of our study is to evaluate the usefulness of ketamine in short pediatric interventions as a safe and applicable method of "dissociative sedation".

Methods: On our retrospective study are included 1527 patients (ASA I-II, 1-15 years old), undergoing inguinal hernia repair, intra-inguinal or intra-abdominal testis retention repair, hydrocele and hypospadias repair. Sedation was realized with ketamine 5mg/kg i.m., atropine 0.015 mg/kg i.m., and midazolam 0.1 mg/kg i.v. Additional doses of ketamine were given in dose 1mg/kg. 3-4 l/O₂ were inhaled with face mask. Monitoring was performed by checking heart rate, respiratory rate, blood pressure and SpO₂, during and 2 hours after surgical intervention. Complications were also noted.

Results: The procedures lasted 19-130 min. Patients were completely emerged 180-250 min. after surgery. Total administered doses of ketamine were 50-200 mg. 95% of the patients were discharged after 6-8 hours. Hypersalivation occurred in 8.2% of cases. It was not

recorded any case of intra or postoperative apnea, obstruction of the airway or stridor. Postoperative nausea and vomiting was reporting only in 6.2% of patients.

Conclusions: Based on our analysis we consider that sedation performed with ketamine, fentanyl and midazolam provides profound analgesia and amnesia with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability. Hospitalization is shorter and the cost of procedure is lower.

MONITORED ANAESTHESIA CARE FOR EXTRACORPOREAL SHOCK WAVES LITHOTRIPSY: PATIENT-CONTROLLED SEDATION VS TARGET-CONTROLLED INFUSION WITH PROPOFOL

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Background and Aims: We studied propofol as unique drug for monitored anaesthesia care during extracorporeal shock-wave lithotripsy (SWL) in order to identify the appropriate and safer method for administering propofol in ambulatory regimen.

Methods: Fifty healthy patients were randomly assigned in two sedation groups. Patients didn't receive any premedication sedative. Three minutes before administering a series of test shock waves one group received propofol with target controlled infusion at 1.5 micrograms/ml, the other group self-administered three boluses of propofol by patient-controlled analgesia (bolus dose 0.3 mg/kg, lockout interval five minutes), (PCS group). Throughout the procedure arterial blood pressure, heart rate, oxygen saturation, and end-tidal CO₂ were recorded. The Observer's Assessment of Alertness and Sedation (OAA/S) scale was used to estimate patient sedation at five minutes intervals till the end of the procedure. Total administration dose of propofol was recorded so as postoperative nausea and vomiting (PONV). The Aldrete score was evaluated at the end of SWL procedure and after one hour in order to estimate patient discharge. Iowa satisfaction with anaesthesia scale's questions was assessed to test patient comfort.

Results: Both groups were hemodynamically stable. PCS group had an increased incidence of desaturation, a major consumption of propofol and some episodes of oversedation.

Conclusions: Both regimens resulted suitable for SWL. TCI group resulted safer and gave a more stable level of sedation during SWL procedure.

COMPARISON OF THE CSM, BIS AND SEDATION SCALES IN VOLUNTEERS DURING PROPOFOL INDUCTION

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Introduction: The CSM delivers the CSI index similar to BIS range from 0 to 100. This study was designed to compare CSM, BIS and the clinical level of sedation during propofol induction.

Methods: After Institutional approval, 25 unpremedicated volunteers were connected to CSM and BIS before starting a propofol TCI infusion with Diprifusor. Propofol was targeted at 0,5 ug/ml and increased 0.5 ug/ml until lose of eye reflex (LER). At every step, a blinded investigator registered the Ramsay scale, OAA/S, CSM, BIS and Ce values. Once the volunteer LER, a 5Hz-5sec tetanic stimuli was administered. Motor and EEG response were evaluated. Later propofol infusion was reduced (0,5 ug/ml steps) and awakening Ce were registered, together with the EEG parameters. The data was analyzed using mean and SD for qualitative variable, with Fisher Test and simple linearity with a significance p<0.05 the Pk according to Smith¹.

Results: At Ce 1.5 ug/ml, Ramsay was 2.83(0,64), OAA/S 3.88(0.45), CSM 80(9.23) and BIS 77(6.52). At LER, Ce was 2.2 ug/ml(0.41), Ramsay 4.25(0.97), OAA/S 2.42(0.79), CSM 66(9.86) and BIS 66(9.77). At waking up time, Ce was 1.88 ug/ml(0.47), CSM 80(12.41) and BIS 75(11.22). All patient has motor response to tetanic stimulus but no change in EEG index response was seen. Except one volunteer. Pk was between 0.7 and 0,95 for the relation CSM/BIS for the different Ce propofol step.

Conclusion: CSM correlates well with BIS values even Clinic, electronic, OAA/S Score and propofol Ce.

THE EFFECT OF A SINGLE DOSE OF ESMOLOL ON THE INDUCTION OF PROPOFOL BY TARGET CONTROLLED INFUSION (TCI)

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Background and Aims:

Esmolol is used to prevent cardiovascular responses during anesthesia at the same time as opiates, reduces the anesthetic requirements. This study was designed to evaluate the induction dose of propofol with and without esmolol pre dosing.

Methods:

We enrolled 60 unpremedicated patients (ASA I-II, 18-60yr) with a BMI between 18-30kg.m² and scheduled for elective surgery under general anesthesia. Patients were randomly assigned to equal three groups by an independent observer. Group I received 20 ml 0.9% saline, Group II received 1mg/kg esmolol diluted to 20 ml and Group III received 2mg/kg esmolol diluted to 20 ml over 60 sec. Three minutes later, the infusion of propofol had been started by using a TCI device to achieve a target plasma propofol concentration of 10µg/ml adjusted to obtain the BIS value between 40-60. When the BIS values arrived to 40 propofol infusion was stopped. Hemodynamic parameters had been recorded during this period in 1min intervals. The further anesthetic management was at the discretion of the attending anesthetist.

Results:

Patient's demographic characteristics and the duration of anesthesia were similar. The mean dose of propofol required in the Group I, II and III to induce anesthesia was 164.1±34.98 ml, 161.05±30.26 ml and 147.06±31.08 ml, respectively (p>0.05). The percentage changes from baseline in heart rate and blood pressure following induction of anesthesia were similar for each group and the difference between groups was not significant. No intraoperative recall was reported.

Conclusions:

Propofol administration by a TCI system results with the appropriate induction doses of propofol providing an adequate level of hypnosis. The administration of 1-2 mg/kg esmolol prior to induction had no significant effect on induction dose of propofol.

DESFLURANE OR TCI PROPOFOL? RECOVERY PROFILE AND SIDE EFFECTS OF REMIFENTANIL-BASED ANAESTHESIA WITH DESFLURANE OR PROPOFOL

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Background: The aim of this ongoing study is to compare the clinical properties of two anaesthetic regimens based on remifentanil in conjunction with either propofol or desflurane with special regard to recovery profile from anaesthesia in patients undergoing Ear–Nose–Throat Surgery.

Methods: Fourteen healthy patients were assigned to receive remifentanil-based anaesthesia in conjunction with propofol (n=7) or desflurane (n=7). Standard monitoring includes electrocardiogram, noninvasive blood pressure, pulse oximetry, and bispectral index (BIS). After standardised induction of anaesthesia (3 ng/mL and 4 mcg/ml effect site concentrations of remifentanil and propofol with TCI infusion system), analgesia is maintained with unchanged remifentanil concentration at a 3.0 ng/ml Ce. Tracheal intubation is facilitated by rocuronium 0.6 mg/kg. For maintenance of hypnosis, propofol (±0,5 ng/ml) or desflurane (±%1 volume) are used in concentrations to ensure BIS 50 +/- 10. Early emergence is assessed by determining the time to adequate respiration, squeezing the doctor's hand, eye opening, extubation, response to verbal command, and recall of date of birth. Recovery is assessed by determining the time to obtain an Aldrette score (ARS) of 10. Duration of surgery, anesthesia, total dose of propofol and remifentanil used are obtained.

Results: Most of the patients opened their eyes, started to breathe and were extubated at the same time, and were immediately orientated verbally, hence no different time were noted for the above mentioned events for most patients. Early emergence from anesthesia did not differ between the groups. There was not any significant difference in obtaining an ARS of 10.

ASSESSMENT OF DEPTH OF ANESTHESIA AND POSTOPERATIVE RECOVERY AFTER REMIFENTANIL VERSUS FENTANYL-BASED TARGET CONTROL INFUSION PROPOFOL ANESTHESIA

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Background: Ongoing study is designed to test the hypothesis that target control infusion (TCI) with equipotent infusion schemes for remifentanil and fentanyl would ensure appropriate analgesia, and an equal depth of anesthesia and remifentanil administration would result in better recovery.

Methods: Up to date 24 healthy patients scheduled for elective septo-rhinoplasty were enrolled in this study. Patients were assigned as the following: remifentanil/propofol (n=14), or fentanyl/propofol

(n=10). Standard monitoring included electrocardiogram, noninvasive blood pressure, pulse oximetry, and bispectral index (BIS). After loading boluses of remifentanyl 1 mcg/kg, or fentanyl 3 mcg/kg was injected, the continuous infusion remifentanyl or fentanyl was started at a rate of 0,15 mcg/kg/min or 0,03 mcg/kg/min respectively. Propofol infusion was then commenced with a 3 mcg/ml effect site concentration (Ce) by means of a TCI device. Tracheal intubation was facilitated by rocuronium 0.6 mg/kg. Remifentanyl and fentanyl infusion rates were maintained unchanged while the Ce propofol was adjusted ($\pm 0,5$ mcg/ml) in order to keep BIS 50 \pm 10. The time from stopping the propofol infusion until the patients opened their eyes, underwent tracheal extubation and their Aldrette recovery scorings (ARS) were also documented.

Results: Both groups revealed hemodynamics within an acceptable clinical range with no significant difference between each other. Time until extubation was not different for both groups; however time for eye opening was significantly different ($p < 0.05$). In remifentanyl group the total dose of propofol was revealed to be lower; but ARS at extubation was higher than that of fentanyl group ($p < 0.05$).

ANALGESIA BASED SEDATION IN PACU: REMIFENTANIL + MIDAZOLAM VS FENTANYL + MIDAZOLAM: PRELIMINARY DATA

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Introduction: Analgesia and sedation are essential in patients admitted to ICU for the following, principal reasons: to control pain, state of anxiety, induce amnesia, improve their adaptation to mechanical ventilation, make invasive procedures tolerable.

Goals: The aim of our study is to compare Remifentanyl-Midazolam(R+M) and Fentanyl-Midazolam(F+M) for analgesia based sedation in PACU.

Methods: We take a group homogenous of 50 patients regard to gender, age, weight and pathology (post operative patients). One group (Grp R+M = 25 pts) received Remifentanyl (6-12 mcg/kg/h) + Midazolam (0.02-0.04 mg/kg/h), the other one (Grp F+M = 25 pts) received Fentanyl (1-2 mcg/kg/h) + Midazolam (0.02-0.04 mg/kg/h). In both groups we controlled deep sedation with SAS and BIS; analgesia evaluating by VAS.

Results: In both these groups there was a good deep sedation (SAS 3, BIS 65 \pm 5, VAS 7 \pm 1). We observed that the patients of the first group (R+M) needed a less dose of midazolam (0.02 mg/kg/h) than the patients of the second group (F+M) (0.04 mg/kg/h). The weaning process to extubation time of the second group was longer than the first one.

Conclusions: Remifentanyl allows a more rapid emergence from sedation, no evidence of accumulation, facilitates earlier extubation and quicker PACU discharge that contribute in cost reduction.

References:

- Breen D. Crit Care 2004 Feb ; 8 R 1- R 11
- Muellejans B. et al. Crit Care 2006;10 R 91
- Park G. et al. Br J Anaesth 2007 Jan ;98 (1) : 76-82
- Karabinis A. et al. Crit. Care 2004 ; R 268-80

REPAIR OF A GIANT INFLAMMATORY ABDOMINAL AORTIC ANEURYSM: ANAESTHETIC IMPLICATIONS

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Background: Inflammatory abdominal aortic aneurysms (IAAA) are described as a distinct clinical syndrome, characterised by thickened aneurysmal wall and adhesion to the adjacent viscera. Surgical repair of these aneurysms carries a mortality of 4.2% to 12.5% and morbidity of 15%. The anaesthetic management of such cases can be quite challenging due to the haemodynamic and metabolic changes that occur during the surgical procedure in addition to the co-existing medical conditions in the patient. We describe the anaesthetic management of a case of giant IAAA.

Case: A 78 year old male who presented with urinary symptoms was found to have an inflammatory abdominal aortic aneurysm measuring 13.7 cms on CT with signs of perianeurysmal fibrosis. At the time of admission for surgery, his aneurysm measured 16cms. General endotracheal anaesthesia with remifentanyl, isoflurane and thoracic epidural were used for this procedure. Remifentanyl infusion was started at the beginning of induction. Boluses of remifentanyl were also used to attenuate hypertensive episodes during laryngoscopy, intubation, cross clamping and other potent surgical stimulus. Use of remifentanyl helped maintain haemodynamic stability throughout the procedure, which was essential in this case as the risk of

rupture increases with hypertensive episodes. Cell salvage was used to reduce the need for transfusion.

Discussion: The advantages of using Remifentanyl in the management of this patient were that it helped achieve haemodynamic stability, partially attenuated the neuro-humoral stress response, reduced the dose requirements of other anaesthetic drugs and quickened awakening thereby enabling early extubation.

DECREASE IN ENTROPY INDEX DURING HEMORRHAGE: EVIDENCE OF ACUTE ALTERATIONS OF PROPOFOL-REMIFENTANIL PHARMACOKINETICS

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Background: Entropy-derived data may provide early insights into altered drug pharmacokinetics and guide drug administration during hemorrhage.

Case Report:

A 62-yr-old man was admitted for abdominal aortic aneurysm repair. History was unremarkable. Anesthesia was performed with target infusion of Propofol (Marsh model) and of Remifentanyl. Routine monitoring was supplemented with Entropy. A stable level of anesthesia was maintained with Entropy of 35-40. Intraoperatively patient was hemodynamically stable. An aortic graft was inserted, with a cross clamp time of 65 min. After unclumping patient's Entropy level began to decrease to a value of 16, before other monitored variables, and burst suppression pattern increased to 48%. About few minutes later blood pressure was < 60 mmHg. Surgeons reported major bleeding. Patient's blood pressure normalized with aggressive volume resuscitation, inotrope therapy and decrease in propofol and remifentanyl target concentrations. Surgical hemostasis proved successful. Patient was admitted in ICU and discharged after 24 h with hemodynamic stability and without neurological impairment.

Conclusion:

It is not clear in this case whether the decrease in Entropy was related only to altered drug pharmacokinetics (increased concentrations) or perhaps also to altered pharmacodynamics (increased sensitivity). Intraoperative acute hypovolemia may result in altered depth as a result of changes in drug disposition; early detection of these changes may have implications for the patient's clinical well-being. Entropy classifies the occurrence of burst suppression as increasing anesthetic drug effect and may offer an approach to titrating the appropriate dose of anesthetic

during hemorrhage when the consequences of overdosing can be unpredictable.

CONTEXT SENSITIVE HALF TIMES AFTER TARGET CONTROLLED PROPOFOL INFUSION

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The context sensitive half time (CSHT) provides information about the decline of plasma drug concentration after a constant infusion for a given duration. We compared CSHT of propofol determined by measured plasma concentrations with that derived by computer simulation for infusions up to 20 hours.

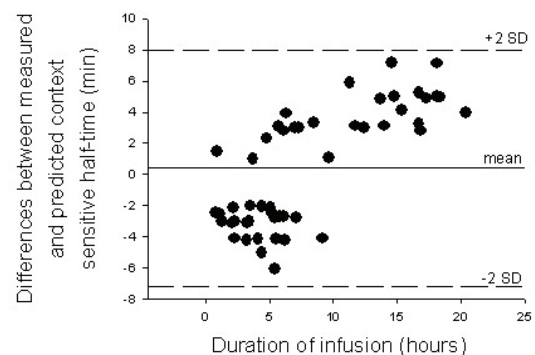
Methods:

After ethics committee approval, written informed consent was obtained from 50 patients undergoing craniotomy. Anesthesia was maintained with target controlled infusions of propofol and remifentanyl. The target concentration before stopping infusion was 3µg/ml. Arterial blood samples were collected for propofol assay after termination of infusion. The predicted CSHT was determined by computer simulation using Marsh parameters. The measured CSHT was determined by fitting propofol concentration-time data with tri-exponential curve. The performance of calculated CSHTs was compared with measured CSHTs using t test.

Results:

The difference between calculated and measured CSHT versus duration of infusion is shown in Figure 1. Calculated CSHT underestimated measured CSHT when propofol infusion was given for less than 10 hours, whereas calculated CSHT was higher than actual value after long hours of infusion. However, the difference was small (P=0.43). The overall bias+/-precision was 0.4+/-3.7 min.

Conclusion: The calculated CSHT for propofol accurately predicts the decline of actual plasma concentration.



TCI FENTANYL VS REMIFENTANIL FOR 4-10 HOUR CASES--SIMULATIONS BASED ON RESPONSE SURFACE MODELS

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Background & Aims:

With the increased use of motor evoked potentials, anesthetics must be conducted without muscle relaxants. To minimize the potential for movement, higher anesthetic concentrations are required. We performed simulations of hypnotic-opioid anesthetics of various durations to determine the optimal target concentration pairs for TCI that would provide clinically adequate anesthesia and the fastest awakening.

Methods:

Response surface models describing the interaction between sevoflurane-remifentanil, propofol-remifentanil, sevoflurane-fentanyl, and propofol-fentanyl in preventing response to tetanic stimulation and to sedation were generated and used to determine a variety of opioid/sedative combinations that produced clinically adequate anesthesia. Published pharmacokinetic models were used to simulate TCI dosing regimens that would maintain effect site concentrations predicted by the RSM to produce clinically adequate anesthesia, across the entire range of opioid-hypnotic combinations. These simulations were used to identify the TCI targets that yielded the fastest awakening from 0.5-10 hour anesthetics.

Results:

The optimal target concentration pairs and time to awakening are shown in the table.

Conclusions:

These simulations demonstrate that using TCI fentanyl to avoid the need for neuromuscular blockade will require high concentrations of sevoflurane that may preclude accurate evoked potential monitoring. In contrast, the optimal concentration pairs of remifentanil-sevoflurane avoid concentrations above 0.5 MAC. The optimal target concentration pairs of fentanyl-hypnotic also produce prohibitively long times to awakening.

Duration	Sevo-Remi ET% : ng/mL (min)	Sevo-Fent ET% : µg/mL (min)	Prop-Remi µg/mL : ng/mL (min)	Prop-Fent µg/mL : µg/mL (min)
0.5 Hr	1.1:4.1 (4.5)	2.5:0.6 (9.4)	1.5:9.2 (10)	2.1:2.0 (24)
1 Hr	1.1:4.3 (5.0)	2.4:0.6 (11)	1.1:12.9 (11)	2.2:2.1 (30)
2 Hr	0.93:4.9 (5.8)	2.5:0.6 (17)	1.0:14.8 (12)	2.2:2.0 (43)
4 Hr	0.88:5.2 (6.7)	2.4:0.6 (32)	1.0:14.8 (14)	2.5:1.7 (83)
7 Hr	0.75:6.1 (7.2)	2.5:0.6 (65)	1.0:14.8 (15)	2.5:1.7 (165)
10 Hr	0.75:6.1 (7.4)	2.5:0.6 (65)	1.0:14.8 (15)	2.5:1.7 (208)

Sevo [ET%] or Prop [µg/mL]; Remi [ng/mL] or Fent [µg/mL] (Time to Awakening [min])

COMPARISON OF THE POTENCY OF PROPOFOL LCT/MCT WITH THAT OF PROPOFOL LCT

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Background and Aims:

Several studies showed that propofol with emulsion of long-chain/medium-chain triglycerides (LCT/MCT) caused less injection pain compared with propofol with emulsion of only long-chain triglycerides (LCT). This phenomenon seemed to be due to the decreased propofol concentration in the aqueous phase. This property might cause the difference in the potency. Here we investigated the effect-site concentration (Ce) at loss of consciousness (LOC) in these two propofol products.

Methods:

After IRB approval and obtained informed consent, we enrolled 40 patients (ASA PS I-II, aged 23-79, either gender) who were scheduled for elective surgery. Patients were assigned into two groups (n=20 each); propofol (LCT/MCT) as group M and propofol (LCT) as group L. Ce of propofol was gradually increased (0.2-0.4 µg/ml/min) using target-controlled infusion system (ConGrase) developed by one of the authors. LOC was confirmed by both no response to call name and loss of eyelash reflex. Using logistic regression, we calculated the Ce50 for LOC.

Results:

As to the demographic data, there were no statistical differences between the two groups. Ce50 at LOC was 1.81 µg/ml (Group L) and 1.99 µg/ml (Group M), respectively. There was no statistical difference between the two groups. When the logistic regression curve of Group M was adjusted by the ratio of Ce50s (namely 0.91), two regression curves became almost identical.

Conclusion:

Although there was no statistical difference, it would be better to conclude that the potency of propofol

(LCT/MCT) was about 0.9 times of propofol (LCT) in getting LOC.

MONITORING OF PROPOFOL IN BREATHING GAS USING ELECTROCHEMICAL SENSOR SYSTEMS

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Background:

During TIVA information about predicted drug plasma concentrations can be derived from pharmacokinetic models. Recent studies have shown that low concentrations of propofol can be detected in exhaled breath during anesthesia providing measured information about plasma concentrations. The results of these studies suggest that online monitoring of propofol breathing gas may become a valuable and convenient tool for the assessment and guidance of anesthesia.

Methods:

In an animal study electrochemical sensors were used to quantify propofol in breathing gas during i.v. anesthesia. Furthermore concentrations of propofol in breathing gas were determined with Gas Chromatography/Mass spectrometry (GC/MS) and plasma concentrations were determined with High Performance Liquid Chromatography (HPLC).

Results:

The acquired sensor data reflects the time course of changing propofol concentrations as confirmed by GC/MS measurements. Regression analysis for each individual animal reveals a correlation of plasma concentrations with breathing gas concentrations. (Range of r values: 0.53-0.98 for HPLC and GC/MS measurements).

Conclusions:

The results of the study indicate that online monitoring of propofol in breathing gas may become feasible in the clinical setting using electrochemical gas sensor technology.

	Pk
CSM/BIS basal	0.75
CSM/BIS 0.5	0.66
CSM/BIS 1.0	0.76
CSM/BIS 1.5	0.87
CSM/BIS 2.0	0.89
CSM/BIS 2.5	0.95
CSM/BISp.r (LOC)	0.77
CSM/BISr.c (ROC)	0.85

PROPOFOL-REMIFENTANIL ANESTHESIA FOR INTRAOPERATIVE WAKE-UP TEST IN SCOLIOSIS SURGERY

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Background and Aims:

Wake-up test is one of the monitors for spinal cord motor function during surgery. Although anesthesia with propofol target controlled infusion (TCI) and repetitive boluses of fentanyl have been used for the surgery requiring the test, remifentanyl would be also useful because of its short action. We report 4 cases anesthetized with propofol TCI plus remifentanyl during scoliosis surgery requiring intraoperative wake-up test.

Methods:

We studied 4 patients (2 males, 2 females, age 12-18 yrs) undergoing scoliosis surgery. Anesthesia was maintained with propofol TCI (plasma concentration 2-3.5 mcg/ml) and continuous infusion of remifentanyl (0.2-0.8 mcg/kg/min) at a rate to keep Bispectral index (BIS) <60. Vecuronium bromide was given intermittently. At the time of wake-up test, the patients were asked to move their foot every 60s. Propofol effect-site concentrations, BIS values, and remifentanyl dosages were recorded.

Results:

Wake-up time was within 25 minutes and BIS values were 89 - 93 at waking up in all patients. Intraoperative wake-up tests were completed successfully (good response) in 2 patients and failed (exciting) in 2 patients. In the successful patients, propofol effect-site concentrations were 0.8 and 1.8 mcg/mL and

remifentanyl dosages were more than 0.2 mcg/kg/min. In failed patients, propofol effect-site concentrations were 0.7 and 1.1 mcg/mL and remifentanyl dosages were less than 0.2 mcg/kg/min.

Conclusion:

Propofol TCI and remifentanyl anesthesia may be useful for the intraoperative wake-up test, while remifentanyl dosage would be needed more than 0.2 mcg/kg/min.

NOVEL INFUSION METHOD FOR DEXMEDETOMIDINE IN THE GENERAL WARD

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We tested our hypothesis using DEX safely and effectively even in the general wards.

Methods:

With IRB approval, 25 gynecological open abdominal surgery patients were randomly and double-blindly allocated: DEX-H (1.0 mcg/kg/hr DEX infusion, n=5), DEX-M (initial 2 hour 1.0 mcg/kg/hr loading then 0.6 mcg/kg/hr infusion, n=5), DEX-L(+) (initial 1 hour 1.0 mcg/kg/hr loading then 0.3-0.4 mcg/kg/hr infusion, n=5), DEX-L(-) (0.3-0.4 mcg/kg/hr infusion, n=5) and placebo (pure saline infusion, n=5). Once the patient was extubated, we started the IV DEX infusion with the Syrinjector® pump (Daiken, Japan). We measured NIBP, HR, respiration rates, SpO₂, verbal response scale (VRS), Ramsay Score, DEX blood concentration at 1 hr and 10 hr after infusion in DEX-L(+) and L(-) groups.

Results:

HR was significantly less in the DEX-H vs. both DEX-L and the placebo. VRS was significantly less in all DEX groups vs. the placebo. Ramsay Score was significantly high in the DEX-H vs. both DEX-L(+)(-) and the placebo. The total dose of Pentazosine for rescue pain was significantly high in the placebo and Hydroxyzine as rescue sedatives was significantly less in all DEX groups vs. the placebo. DEX blood concentration at 1 hr and 10 hr after infusion in DEX-L(-) was 0.18ng/ml and 0.48ng/ml (mean), in DEX-L(+)group was 0.58ng/ml and 0.46ng/ml (mean).

Conclusions:

The DEX-L(+) and L(-) showed that VRS significantly less and no significant change in HR, MBP and Ramsay Score vs. placebo group. Because of loading regimen,

DEX blood concentration in L(+) achieving effective concentration earlier and showed best results.

TCI WITH PROPOFOL/RÉMIFENTANIL DURING LAPAROSCOPIC SURGERY OF OBESITY

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Introduction:

The generalization of the TCI leads to its use among patients too different from the population which was used to determine the model. This passes obligatorily by a clinical validation as it was the case for the old subjects or the ethyl ones (Anesthesiology 2003; 99:576 - 85). The purpose of the study is to evaluate the clinical feasibility of the propofol/rémifentanil TCI at a homogeneous population of obese.

Material and Methods:

Open exploratory study among 30 obese patients (BMI>35). average age 32±4 years. Type of surgery: by-pass. Anaesthetic induction: propofol cerebral target 6 ng/ml according to the model of schneider. Dice the LOC, the rémifentanil is injected(CE= 4ng/ml). After stabilization of the CE the succinylcholine is managed to facilitate intubation. After intubation the propofol CE is fixed has 2,5 mg/ml and that of rémifentanil is adapted according to the hemodynamic parameters (BP and HR maintained enters 80% and 120% of the values of bases)

Results:

	breathing	openingeyes	extubation	exit
Time(mn)	9	13	14	30
CEprop(mg/ml)	0,7	0,5	0,5	0,3
CErémidf(ng/ml)	1,7	1,2	0,9	0,5

Discussion:

Our study shows that TCI appears a technique adapted well to the requirements of the surgery of obesity. The use of a cerebral target allows a fast induction without major incidents for all the patients. The necessary concentrations of propofol and rémifentanil are different from those published among not obese patients.

Conclusion:

The determination of models adapted for this population could improve the performance of propofol/rémifentanil TCI.

THE SCHNIDER MODEL MUST BE BALANCED ACCORDING TO THE GENDER

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Introduction:

The model of Schneider offers a better precision and facilitate the use of the the propofol TCI while avoiding with the clinician adapting the target concentrations to the age and the BMI. The purpose is to determine CE_{loc} and CE₅₀ of tracheal intubation (CE_{50int}) with propofol (associated with fentanyl) according to Schnider model for men(M) and woman(W).

Materials and Methods:

40 patients, ASA 1 or 2, proposed for abdominal surgery were randomized in two groups (group M, group W). 3mn after fentanyl (3mcg /kg), TCI of propofol using the Schnider model. For the first patient of each group we uses CE=5mg/l. The CE used for the following patient is given according to the method up and down of DIXON and the quality of anaesthesia of the preceding patient at the time of intubation: If the anaesthesia is adequate the effect CE is decreased by 0,4mg/l for the following patient and conversely. For each patient we noted CE_{loc} and CE_{int}. RESULTS: The CE_{50int} was 5,28± 0,16 and 3,94±0,35 respectively in the groups M and W(p=0.0253) .The LOC occurred with 2,79 ±0,55 µg/ml for w and 3,86 ± 0,81 for M(p=0,0482).

Discussion:

The use of the TCI which takes into account several covariables (age, weight, size, BMI) could easily highlight the PKPD differences between the two sexes (M.Kodaka, Anesth Analg 2005).

Conclusion:

TI with propofol TCI with the Schnider model is done at the M and the W by using different target concentrations. The Schnider model would not be thus completely independent of the gender.

SURVEY OF PRACTICES OF ADMINISTRATION OF TIVA-TCI IN A NORTHERN REGION OF THE UNITED KINGDOM

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Background: Reuse of syringes and infusion sets for TIVA have been implicated in outbreaks of sepsis and pose a potential risk for blood borne infections. Specific

guidelines from manufacturers of TIVA administration sets and guidelines from the Royal college of Anaesthetists and the Medical Devices agency advice against reuse of equipment. The efficacy of antireflux and one way valves is not backed by clinical data. We conducted a regional postal survey to identify practices of TIVA administration and assess awareness of infection risks.

Methods: A questionnaire was sent to all consultants in the Northwest region of UK. Questions concerned the type of delivery system, reuse of administration systems and awareness of guidelines.

Results: The response rate was 40.9%. Most respondents used dedicated sets for administering TIVA. Although 91% of them used non return valves only 24 % used them at both distal and proximal ends. 62.4% anaesthetists would change syringes and tubings between patients and the others would change various parts of the administration system but not the syringes. 94.4 % of anaesthetists would not reuse any part of the system from a patient with known blood borne disease .Reasons for reusing were cost (35.2%), ease (20 %) and speed (20%) of set up. Only 16 % anaesthetists were aware of any guidelines concerning reuse of TIVA equipment.

Conclusion: There is a wide variation of practices for administration of TIVA which may increase infection risk for patients. Only 62.4% anaesthetists follow manufacturer guidelines for single use of all TIVA equipment.

ENTROPY OF EEG FOR THE MONITORING OF PROPOFOL-INDUCED HYPNOSIS

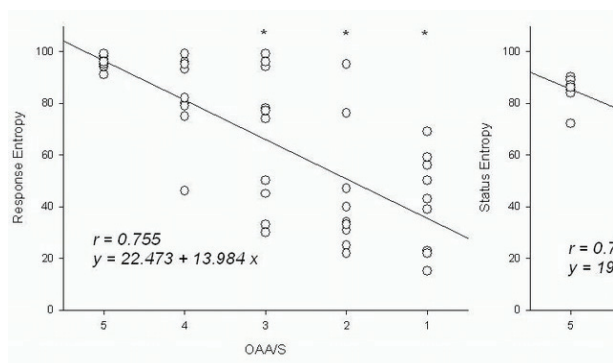
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To evaluate EEG entropy's ability to determine all levels of sedation, effect concentration of target-controlled infusion (TCI) of propofol was set 1.0 µg/ml and increased by 0.5 µg/ml every 20 sec to reach 4.0 µg/ml or BIS score < 60 during anesthesia induction (n = 12). Status entropy (SE) and response entropy (RE) corresponding to Observer's Assessment of Alertness/Sedation score (OAA/S) 5 to 1 were determined.

While RE and SE values showed significant correlation with OAA/S and those corresponding to OAA/S 3 to 1 were different from those corresponding to OAA/S score 5 (p < 0.05), those to OAA/S 4 was not different from those to OAA/S 5.

EEG entropy was not able to distinguish the light level of sedation from alert status.



EFFECT OF PROPOFOL ON CALCIUM HOMEOSTASIS IN HYPOXIA-REOXYGENATED NEONATAL RAT CARDIOMYOCYTES

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The intracellular calcium homeostasis must be carefully regulated by specific binding, transport proteins and ion channels. Intracellular calcium overload, as a consequence of abnormal calcium homeostasis, is a major cause of ischemia-reperfusion (I/R) injury in the heart. Propofol is a widely used intravenous anesthetic and has been shown to attenuate ischemia-reperfusion injury. This benefit action of propofol has been mediated by free radical scavenging and inhibition of plasma membrane calcium channel, but the effects of propofol on calcium homeostasis in response to hypoxia-reoxygenation have not been reported. In the present study, the effects of propofol on calcium homeostasis were investigated by evaluating the expression of genes coding for calcium-handling proteins (calreticulin, calmodulin, calsequestrin, PMCA1), sarcolemmal L-type calcium channels, sarcoplasmic reticulum calcium cycling proteins (ryanodine receptor, SERCA2a, phospholamban) and ion exchangers (NCX) in hypoxia-reoxygenated neonatal rat cardiomyocytes. We observed that propofol increased the survival rate and induced a significant increase in the transcript level of calcium-handling proteins and SERCA2a. These results indicate that propofol promotes calcium transport into the sarcoplasmic reticulum and helps maintain intracellular calcium content during hypoxia-

reoxygenation. This may provide new insight into myocardial protection by propofol.

QUANTITATIVE EVALUATION OF NEUROPROTECTIVE EFFECTS AFFORDED BY THIOPENTAL AND PROPOFOL ON BRAIN ISCHEMIA

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Background and Aims: Anesthetics are known to have some neuroprotective effects on brain ischemia. In the present study, we quantitatively evaluated the neuroprotective effects of thiopental, propofol and halothane on brain ischemia by determining the ischemic time necessary for causing 50% neuronal damage (P50). Extracellular Glutamate concentrations during ischemia were also measured.

Methods: Seventy-eight gerbils were used. In the thiopental group (n=26) and propofol group (n=26), thiopental and propofol, respectively, were continuously infused intravenously to produce a burst suppression pattern of EEG. In the halothane group (n=26), halothane was maintained at 1%. Brain ischemia was initiated by 2-vessel occlusion for a pre-determined duration (3, 5 or 10 min, n=7 in each group). Histological evaluation of bilateral CA1 regions was performed 5 days later. Extracellular glutamate concentrations during 7.5 minutes of ischemia were measured using microdialysis method (n=5 in each group).

Results: P50 was calculated to be 5.1 min in the halothane group, 6.5 min in the propofol group ($p < 0.05$ compared with halothane) and 8.4 min in the thiopental group ($p < 0.05$ compared with halothane and propofol). Maximum glutamate concentration in the thiopental group ($33 \pm 10 \mu\text{mol/L}$) was significantly reduced compared with that in the halothane group ($88 \pm 34 \mu\text{mol/L}$, $p < 0.01$) and tended to be lower than that in the propofol group ($52 \pm 8 \mu\text{mol/L}$, $p = 0.16$).

Conclusions: P50 in the thiopental and propofol groups was prolonged by 165% and 127%, respectively, of that in the halothane group. Attenuation of glutamate accumulation during ischemia seems to be involved in the mechanism of neuroprotection afforded by thiopental.

COMBINATION OF PROPOFOL AND DEXMEDETOMIDINE FOR SEDATION AFTER CARDIAC SURGERY IN ICU

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The purpose of this observational study was to simulate the blood concentration of propofol and dexmedetomidine during postoperative ventilatory support in patients after cardiovascular surgery.

Twenty-five patients who admitted ICU and mechanically ventilated after major cardiovascular surgery were sedated with the combination of propofol and dexmedetomidine. After the patients respond the verbal command, propofol infusion was initiated and the dose of propofol was titrated to achieve Ramsey sedation scale (RSS)=5. If the dose exceeds 2mg/kg/hr, the dexmedetomidine infusion without loading dose was initiated and titrated to achieve RSS=5. During the weaning process, the target RSS was reduced to 3 and the dose of propofol was titrated. The blood concentration was simulated with the Rugloop software using pharmacokinetic data from Marsh and Vuyk.

Data from 16 male and 9 female (age; 59±13 y/o) were expressed as mean±SD and were summarized in the table.

Co-administration of propofol and dexmedetomidine could achieve equivalent sedation with lower dose and blood concentration compared with the monotherapy. This synergism may be advantageous to achieve stable sedation while circumvent the possible side effects of the two drugs such as hemodynamic stability, respiratory depression and metabolic disturbances.

	Dose	Plasma conc.
Target RSS=5		
Propofol	1.68±0.67 mg/kg/hr	0.91±0.37 µg/ml
Dexmedetomidine	0.34±0.15 µg/kg/hr	0.38±0.20 ng/ml
Target RSS=3		
Propofol	1.24±0.57 mg/kg/hr	0.49±0.22 µg/ml
Dexmedetomidine	0.34±0.15 µg/kg/hr	0.44±0.21 ng/ml

BIS MONITOR IN HYPERCAPNEA, ANOTHER POSSIBLE APPLICATION OF BIS

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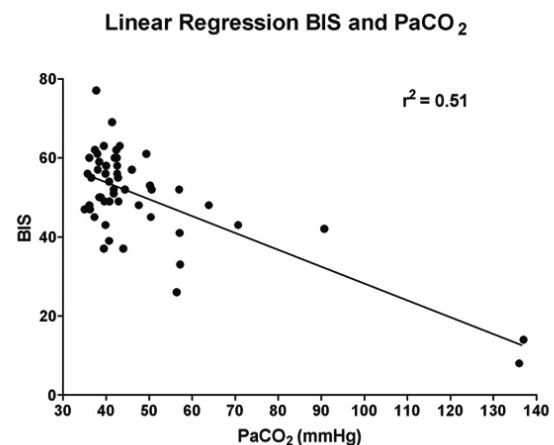
Patient safety is essential for modern anesthesia practice. Bispectral index is valuable for CNS monitoring

especially hypnotic level. We report another possible application of BIS.

Method: All patients studied were over 70 years old. General anesthesia was induced and maintained with propofol (5 or 6 mg/kg/hr), ketamine (0.5 mg/kg/hr) and fentanyl. Bispectral index was monitored with BIS monitor (Model A-1050, Aspect medical system inc. MA, USA). A total 51 points were analyzed. Correlation was calculated among BIS (50.4 +/- 12.2; mean +/- S.D.), body temperature (35.6 +/- 0.7 OC), and PaCO₂ (48.1 +/- 20.6 mmHg)

Results: BIS value were decreased accompanied with increase in PaCO₂ (r²=0.517, p<0.0001). There were no significant relations between BIS and body temperature, nor BIS and PaCO₂

Conclusion: We propose that BIS is not useful monitor of sedation but also a valuable tool to predict excess hypercapnea-induced CNS sequelae. Therefore, BIS will provide helpful information of patient safety to anesthesiologist.



TARGET CONTROLLED INFUSION OF REMIFENTANIL IN MORBIDLY OBESE PATIENTS: PURSUING THE BEST WEIGHT INPUT CORRECTION

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Background:

There are some concerns regarding the right weight input for remifentanil TCI in morbidly obese patients, since Lean Body Mass (LBM), which turned out to be a significant covariate for central and rapid peripheral

compartments, and also for metabolic clearance, is defined by equations with an odd property. In particular, up to a certain weight, which can be called “Critical Weight” (CW), there is an increase in LBM as Total Body Weight (TBW) increases; however, after the weight that corresponds to the peak LBM value (i.e. CW, specific for height and gender), further increases in TBW correspond to a decrease in LBM values. The wrong estimation of LBM causes substantial invalidation of this pharmacokinetic set in morbidly obese patients, thus TBW cannot be used as weight input in this class of patient.

Methods:

A reasonable approach is to believe that that LBM increases with TBW up to a certain point, beyond which there is virtually no clinically significant increase in LBM for every increase in TBW. If we admit that this critical point corresponds to the weight at which the LBM function peaks (i.e. the CW), then it is the CW that must be used if our patients weigh more than it.

Results:

With a simple mathematical estimation, the CW can be derived both for men and for women:

$$CW(\text{men})=1.447*\text{Height}(\text{cm})-121$$

$$CW(\text{women})=1.211*\text{Height}(\text{cm})-101$$

Conclusions: Correcting the weight input according to the Critical Weight could be the right choice in order to use remifentanyl Target Controlled Infusion in morbidly obese patients.

HOW TO CORRECT MINTO’S PHARMACOKINETIC SET IN MORBIDLY OBESE PATIENTS: THE “FICTITIOUS HEIGHT” IN MEN (I)

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Background:

There are some concerns regarding weight input for remifentanyl TCI in morbidly obese patients, since Lean Body Mass (LBM), which turned out to be a significant covariate for central and rapid peripheral compartments, and also for metabolic clearance, is defined by equations that have an odd property.

Methods:

Since for this model the significant covariate is LBM only (not weight and height incorporated separately), it

is possible to use a “fictitious height” in order to have the right LBM value calculated and used for the pharmacokinetic model-driven infusion while using the patient’s total body weight as input weight. This way, the calculated LBM value corresponds to the value that would be obtained with a DXA scan in the same individual.

Results:

The equation was derived with a simple mathematical process and is shown in Figure 1.

Conclusions:

This equations corrects Minto’s pharmacokinetic set in morbidly obese male patients.

$$h_{\text{Fict}}(\text{men}) = \sqrt{\frac{128 \times TBW \times (6.68 \times 10^3 + 216 \times BMI)}{-1922 + 1.1 \times 216 \times BMI}}$$

Figure 1: how to calculate the fictitious height (h_{Fict}) in men. TBW stands for total body weight and LBM for body mass index

WEIGHT INPUT FOR TARGET CONTROLLED INFUSION OF REMIFENTANIL IN MORBIDLY OBESE PATIENTS: TESTING A POSSIBLE CORRECTION

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Background: Even though for remifentanyl Target Controlled Infusion (TCI) the input weight should not be corrected, in fact a correction is needed in morbidly obese patients, since the Lean Body Mass (LBM) formula reveals an odd property in these patients.

Methods: We focused on a 40 year-old obese female patient, weighing 205 kg, 1.70 m tall and a non-obese control patient, aged 40 years, weighing 55 kg, 1.70 m tall, during a simulated Target Controlled administration of remifentanyl of 120 minutes set at 2 ng/ml. In the obese patient, the weight is corrected according to a mathematically derived formula:

$$\text{Input_Weight}=1.211*\text{Height}(\text{cm})-101$$

Results: The effects of this simulation on some parameters of the pharmacokinetic set of Minto, remifentanyl consumption and patients’ demographic features are listed. LBM appears to be 56 kg in the obese patient, compared to 43 kg in the non-obese patient. In the obese patient, V1 is greater than in the non-obese patient (+ 18%), as well as V2 (+ 14%) and Cl1 (+ 9%). In this way a total of amount of 604 µg remifentanyl would be administered to the non-obese

patient, compared to 666 µg (+ 9%) to the obese patient. The additional amount administered to the obese patient reflects the greater value of LBM in this patient.

Conclusions:

The weight correction according to the aforesaid formula is effective in the case of a morbidly obese patient, and could be the right choice for remifentanyl TCI in this particular class of patient.

HOW TO CORRECT MINTO'S PHARMACOKINETIC SET IN MORBIDLY OBESE PATIENTS: THE "FICTITIOUS HEIGHT" IN MEN (II)

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Background:

In the previous abstract we explained how to correct Minto's pharmacokinetic set (PK) in morbidly obese male patients according to the "fictitious height". In this abstract this correction will be tested by means of a simple computer simulation.

Methods:

We focused on a 40 year-old obese male patient, weighing 245 kg, 1.70 m tall and a non-obese control patient, aged 40 years, weighing 70 kg, 1.70 m tall, during a simulated Target Controlled administration of remifentanyl of 120 minutes set at 2 ng/ml. In the obese patient, the weight was corrected according to the mathematically derived formula presented previously.

Results:

Simulations for the morbidly obese patient (unadjusted PK set), control patient and morbidly obese patient (adjusted PK set) are summarized in Table 1.

Conclusions: Changing the input height according to the "fictitious height" corrects Minto's PK set in morbidly obese male patients.

Patients' Demographic Features, Minto's Pharmacokinetic Parameters and Remifentanyl Consumption			
Variable	Obese Patient	Matched Control	Obese (h corrected)
Sex	M	M	M
Age (yr)	40	40	40
Height (m)	1.7	1.7	2.07 (hg)
Weight (kg)	245	70	245
LBM (kg)	3.65	55.30	90.19
BMI (kg/m ²)	84.8	24.2	57.2
V ₁ (l)	1.4025	5.1216	7.6338
V ₂ (l)	4.3822	10.12	13.6205
V ₃ (l)	5.42	5.42	5.42
K ₄₀ (min ⁻¹)	0.5950	0.5950	0.5950
K ₁₀ (min ⁻¹)	1.1545	0.5088	0.4286
K ₁₂ (min ⁻¹)	1.4617	0.4003	0.2685
K ₂₁ (min ⁻¹)	0.4797	0.2081	0.1505
K ₁₃ (min ⁻¹)	0.0542	0.0148	0.0100
K ₃₁ (min ⁻¹)	0.0140	0.0140	0.0140
Cl _l (l/min)	1.6383	2.6057	3.2721
Remi120 (mcg)	408	664	836

Table 1: Patients' demographic features, Minto's pharmacokinetic parameters and remifentanyl consumption of the obese vs non-obese patient for a hypothetical infusion of 120 minutes. The two central columns represent the comparative simulation when no correction is used in the obese patient. The right column shows what happens when the height of the morbidly obese patient has been corrected according to the "fictitious height". It is evident that this corrects the pharmacokinetic set and allows its use despite the fact that it incorporates wrong equations for the calculation of LBM values.

ADEQUATE DOSE OF REMIFENTANIL FOR ENDOTRACHEAL INTUBATION WITH PROPOFOL WITHOUT MUSCLE RELAXANTS

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Background: Many studies have shown that tracheal intubation could be facilitated after induction with propofol and opioids without muscle relaxants. Remifentanyl, which has a rapid onset and ultra-short duration of action, is a useful esterase-metabolized opioid (EMO) for tracheal intubation. This study was designed to evaluate the adequate induction dose of remifentanyl with propofol 1.5 mg/kg for tracheal intubation without muscle relaxants.

Methods: We have assessed intubating conditions in five groups of 57 female patients, ASA PS I or II. Each group was administered intravenous propofol 1.5 mg/kg with remifentanyl 1.0 µg/kg, 2.0 µg/kg, 3.0 µg/kg, 4.0 µg/kg and 5.0 µg/kg, respectively. Intubation was attempted, and the intubating condition was scored by the degrees of relaxation of jaw (0-2), position of vocal cords (0-2) and the patient response (0-2). Mean arterial pressure (MAP) and heart rate (HR) were observed at each group.

Results: The relationship between the concentration of remifentanyl and the possibility of endotracheal intubation was as following: Probit (P) = - 1.38 (S.E.: 0.58) + 0.087 (S.E.:0.23) × DRemi. The ED50 of remifentanyl for endotracheal intubation without muscle relaxants was 2.12 (95% confidence interval: 1.42~2.62)

µg/kg and the ED95 was 4.01 (95% confidence interval: 3.31~5.92) µg/kg.

Conclusions:

We concluded that adequate dose of remifentanil which make possible to endotracheal intubation without muscle relaxants after induction of general anesthesia with 1.5 mg/kg of propofol is 4.01 µg/kg in 95% of female patients and 2.12 µg/kg in 50% of female patients.

EFFECTS OF TIVA WITH PROPOFOL-REMIFENTANIL ON HEMODYNAMIC AND GLOBAL TISSUE OXYGENATION IN PATIENTS UNDERGOING BARIATRIC LAPAROSCOPIC SURGERY

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Background and Aims:

To study the effects of TIVA with propofol-remifentanil(P-R) on hemodynamic and global tissue oxygenation in patients undergoing laparoscopic bariatric surgery.

Methods:

15 consecutive morbidly obese patients (BMI>40 kg/m²) who were undergoing BLS were anesthetized with target controlled infusion of P-R. Target serum concentrations of propofol were adjusted to maintain a BIS value between 40 and 60. Hemodynamic parameters and central venous saturation were obtained continuously using the FloTrack transducer and a central fiberoptic catheter (Vigileo, Edwards Lifesciences).

Results:

Postinduction was observed a decrease in CI(20%), SVR(25%) and CVP(32%), and SVV increased (27%). SvO₂ decrease and lactate levels were not altered. Posterior to step volume loading, hemodynamic parameters improve and remain stable: (CI=2.7±0.2, SVV=6±3, CVP=14±3). GTO as evaluated by SvO₂ and lactate levels did not shown evidence of compromise (SvO₂=78±4, lactate=1.2±0.3).

Conclusions:

TIVA with P-R permit to maintain a stable hemodynamic condition without evidence of compromise in GTO. Hemodynamic monitoring to optimize intravascular volume may be useful to minimize unnecessary volume loading in this limited cardiac reserve patients.

IN ADULTS, BISPECTRAL INDEX AND SPECTRAL ENTROPY DEPEND ON AGE DURING INDUCTION OF ANAESTHESIA WITH PROPOFOL

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Background: BIS and Spectral Entropy (ES) are EEG monitors that are used to quantify the hypnotic effects of anaesthetic drugs. Since EEG is modified by age we aimed to investigate whether age also influences BIS and ES during induction of anaesthesia with propofol.

Methods: Two cohorts were studied: "young" patients (<40 years) and "elderly" (>65 years). All had induction with propofol using a stepwise increase in effect site concentrations until loss of consciousness (LOC)(OAAS score <2). BIS, and state and response ES were recorded before start of propofol administration and after each steady-state propofol concentration until(LOC). A blinded observer assessed the OAAS score throughout induction. Data are presented as means [±SD].

Results: We analysed 34 "young" patients (age range, 19-40 years) and 35 "elderly" patients (range, 67-96 years). Average BIS, and state and response ES values significantly decreased with increasing effect site concentrations of propofol, but independent of age. For LOC, elderly patients required significantly lower effect site concentrations of propofol compared with younger patients (2.48 [0.58] µg ml⁻¹ vs 3.43 [0.57] µg ml⁻¹, p<0.001). At LOC, elderly patients, compared with younger patients, had significantly higher values of BIS (70 [8] vs 55 [9], p<0.001), state ES (70 [15] vs 52 [16], p<0.001), and response ES(78 [15] vs 57 [16], p<0.001).

Conclusions: During induction of anaesthesia with propofol, elderly patients have relatively higher BIS and ES values despite clinical signs of adequate depth of anaesthesia. Age should be considered when quantifying the hypnotic effects of anaesthetic drugs with simplified EEG monitors.

INCIDENCE OF SIGNIFICANT DIFFERENCES IN BIS MEASURED BETWEEN HEMISPHERES DURING BILATERAL BIS MONITORING

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Introduction: We evaluated occurrences of interhemispheric differences in BIS during propofol/alfentanil/N₂O anesthesia.

Methods: We analyzed data from 324 adults undergoing non-cardiac surgery[1]. Sustained Differences (SD) between hemispheres were defined as a interhemispheric difference in BIS (rev3.4) > 5 points lasting at least 1 minute.

Results: BIS provided similar values from both sides of the head (within 5 BIS units) for 95% of each case. Short periods of SD occurred in 41% of patients for 4.6 +/- 9.1 % of case duration. Patients who had at least one SD episode were more likely to be male (55% men vs. 35% women, $p < 0.001$), older (age: 45 +/- 15 vs. 38 +/- 13, $p < 0.001$), and have less EEG total power (dB) (0.5-47Hz) (21.2 +/- 2.8 vs. 22.8 +/- 2.6, $p < 0.001$). EEG total power decreased with increasing age ($R = -0.55$, $p < 0.001$). Weight, ASA Physical Status, and surgical site (i.e., lateralized vs. centralized surgery) were not different between patients who had and did not have SD. SD occurred most frequently during maintenance rather than during induction or emergence.

Conclusions: Sustained differences greater than 5 BIS units for at least 1 minute occur infrequently, but are more likely to be seen in men, the elderly and patients with less total EEG power, and are associated with greater hemispheric differences in SQI. The clinical relevance of such brief differences remain unknown.

Reference:

Anesthesiology 1997; 87(4): 808-15.

VOLATILE VERSUS TOTAL INTRAVENOUS ANAESTHESIA. AN 11 YEAR STUDY OF OUTCOMES FOLLOWING DAY CASE SURGERY AT TORBAY HOSPITAL

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Background & Aims: Minimising anaesthetic complications is a key factor in one day surgery. We aimed to assess the influence of choice of anaesthetic agent on outcomes in Torbay Hospital Day Surgery Unit (DSU)

Method: Database analysis of all patients aged 16 years or over who received a general anaesthetic in Torbay DSU between August 1995 and November 2006. 41350 patients were included of which 9681 received volatile agents and 31669 received TIVA.

Results: 1. Hospital admission rates for anaesthetic complications (nausea, vomiting, dizziness and feeling faint) were 1.22% (n=118) for the volatile group and 0.92% (n=292) for the TIVA group ($p = < 0.01$). Over the study period the use of TIVA increased from 60% of patients in 1996 to 80% in 2005. Over the same period

the anaesthetic related admission rate dropped from 2% to 0.3%. 2. At 24 hour telephone follow up significantly fewer TIVA patients reported nausea, vomiting, drowsiness or dizziness than those who had received Volatile agents ($p < 0.01$).

Conclusions: The fall in admission rate has occurred despite the increasing complexity of our surgical case mix. It is in part due to optimisation of other areas of anaesthetic technique but these results suggest the increasing use of TIVA is also a factor. The reduced incidence of post anaesthetic complications after twenty four hours for patients who received TIVA has major clinical significance. It further supports the available evidence for the use of Propofol TIVA as the first choice anaesthetic technique for day surgery patients.

COMPARISON OF ROCURONIUM PK/PD MODELING AND TRAIN-OF-FOUR PERIPHERAL NERVE STIMULATOR

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Background:

The Navigator Applications Suite (GE Healthcare, Helsinki, Finland) gives Pharmacokinetic/ Pharmacodynamic (PK/PD) models for several drugs (hypnotics, inhaled agents, opioids and neuromuscular blocking drugs) and uses an integrated algorithm based on two models for Rocuronium: the PK model is based on three-compartmental time constants performed by Cooper (1) and the PD model based on the Keo provided by Plaud (2). The second model is available in the Stanpump system (Palo Alto – USA) and this was used as a simulated comparison.

Aim:

The aim of this prospective study is to evaluate the performance of the Plaud model and Navigator Applications Suite model by direct correlation of theoretical effect site concentration compared with a peripheral neuromuscular transmission system and its Train Of Four (TOF) score (percentage of fourth response to the first response, or T1%), using the GE Datex-Ohmeda S/5 Anaesthesia Monitor, M-NMT module and accelerometer mechanosensor (GE Healthcare, Helsinki, Finland).

Method:

12 patients without neuromuscular disease, submitted to TIVA for neurosurgery, were enrolled in the study. Anesthesia was performed in TCI-view modality with the same propofol and remifentanyl targets for all patients, monitored using Navigator Applications Suite.

Neuromuscular blockade was obtained with Rocuronium 0.6 mg/kg under TOF control. Rocuronium bolus was administered by infusion pump connected to the Navigator to create PK/PD trends of effect site concentration (Ce) for rocuronium infusion. T1% values from S/5 AM monitor and Ce values from Navigator Applications Suite were collected every 10 seconds from rocuronium administration to achievement of the maximal response of T1% (100%). Then with Stanpump simulation and the same patient parameters, Ce values by Plaud (PlaudCe) model was recorded every 10 seconds and collected with T1% and Navigator Ce (NavCe) values.

Pearson correlation with 95% Confidence Interval (CI95) between T1% - PlaudCe values and T1% - NavCe values was found. Prediction Probability (pK) with Standard Error of the estimate (SEe) for the two models was calculated by comparing T1-50% evaluated from TOF and the Ce to achieve T1-50% registered from the two systems.

Results:

5 patients were excluded from the study due to TOF system dislocation during data collection. There were 1248 registered data pairs. Pearson correlation between T1% value and PlaudCe was 0.779 (CI95 0.701-0.848), between T1% value and NavCe was 0.827 (CI95 0.781-0.837). PlaudCe pK was 0.903 (SEe 0.026) while NavCe pK was 0.921 (SEe 0.017).

Discussion:

Correlation is high but not total because Ce increase during rocuronium pharmacodynamic action induces "fade" on neuromuscular districts without activation of TOF transduction (T1%=0): so with TOF it's impossible to evaluate all pharmacodynamic rocuronium action, using Post Tetanic Count (PTC) could give some indication on neuromuscular blocking level. The NavCe correlation with TOF is little higher than PlaudCe correlation with TOF and same consideration can be due for pK. There is a good correlation from PK/PD model prevision and the measurement by TOF to the Ce: this is demonstrated by very high pK (near the maximal that is 1). Prevision given by NavCe seems to be clinically better than PlaudCe.

In conclusion, PK/PD rocuronium model directly registered by Navigator during its administration can reduce limitations linked to TOF use during clinical practice and limitations based on indirect simulation systems such as Stanpump.

References:

1. Cooper RA, et al. Br J Anaesth. 1993; 71:222-6.
2. Plaud B, et al. Clin Pharmacol Ther. 1995; 58:185-91.

A CONTRIBUTION OF PALMACOKINETICS TO WIDESPREAD USE OF TIVA IN A REGIONAL UNIVERSITY HOSPITAL IN JAPAN

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Background: PALMACOKINETICS is a simulation software developed by Osamu Uchida M.D., Ph.D. belonged to National Cardiovascular Center Hospital (<http://www.palmacokinetics.com/>) to predict the effect-site concentration (Ce value) of propofol and fentanyl. In regional cities, very few anesthesiologists allow the residents of small experience of anesthesia commit general anesthesia under the direction of small number of attendings. Volatile anesthetics have been widely used for general anesthesia because it is relatively easy to maintain vital signs by changing concentration of anesthetic agents according to the level of arterial blood pressure. Recently it has become known that propofol and fentanyl improve the quality of anesthesia, but TIVA has not been applied because it requires target controlled infusion(TCI) pumps to administrate propofol and fentanyl.

Method: We have had each resident carry PALMACOKINETICS and attempted to commit a general anesthesia with predicting Ce values in each case. [RESULTS] The residents who once acquired the concept of estimating Ce values have come to easily apply TIVA even without PALMACOKINETICS. Some calculated Ce values were different from the real ones in the cases such as obesity and mass bleeding.

Conclusion: PALMACOKINETICS is suggested to be useful for young residents without TCI pumps.

EVALUATION OF REMIFENTANIL TARGET FOR TRACHEAL INTUBATION WITHOUT MUSCLE RELAXANTS IN THYROID SURGERY

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Background and Aims:

In our hospital, thyroid surgery requires tracheal intubation without muscle relaxants in order to monitor

the recurrent nerves with a special tracheal tube (NIM EMG endotracheal tube, Medtronic laboratory). Patients are anaesthetized with total intravenous anaesthesia (TIVA, cerebral target) using propofol and remifentanyl (base Primea Fresenius Vial laboratory). The objective of our study was to evaluate our daily practice and the intubation conditions with various target of remifentanyl.

Methods:

The study was descriptive and unicentric. After enlightened information, 36 patients scheduled for thyroid surgery were prospectively included. Remifentanyl (4, 6 and 8 ng/ml, Minto protocol) was started 4 minutes after propofol (6 µg/ml, Schnider protocol). After tracheal intubation, remifentanyl concentration was half reduced. Tracheal intubation conditions were evaluated with different parameters: laryngologic exposure, condition of mechanical ventilation, positions of the vocal cords, response to intubation and cough. Haemodynamic tolerance was evaluated with non invasive blood pressure and heart rate monitoring every minute during 15 minutes.

Results:

The three groups were comparable in term of ASA score and age. The intubation conditions were significantly different with the 3 remifentanyl concentrations (p=0.0009). However, with the highest concentration, half of the patients have coughed. We noted comparable haemodynamic repercussion in the three groups.

Conclusions:

High target amounts of remifentanyl in TIVA with concentration objective improve the conditions of intubation. High target improved tracheal intubation conditions without raising the haemodynamic risks.

Remifentanyl target (ng/ml)	Excellent	Good	Fair
4	0	2	8
6	7	4	3
8	6	6	0

Table 1 : intubation conditions with various concentrations of remifentanyl

PROPOFOL VERSUS SEVOFLURANE IN ADULT DAY SURGERY: INDUCTION AND RECOVERY CHARACTERISTICS

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Background and Aim of Study:

The aim of this study was to compare induction and recovery characteristics associated with propofol

induction and maintenance with sevoflurane induction and maintenance of anaesthesia in adult female patient (> 18 years) undergoing day surgery of the breast.

Methods:

60 patients undergoing day-surgery were randomly assigned in two groups: to propofol and alfentanil induction and maintenance and sevoflurane and alfentanil induction and maintenance (30 patients in each group). The procedures were shorter than 30 minutes. The times required for induction, maintenance, recovery (obeying commands), postoperative nausea and vomiting during recovery and time discharge home was recorded.

Results:

The mean time required for induction with propofol was 2.9 min compared with 4.9 min in sevoflurane group (p<0.01). No significant differences were detected in maintenance of anaesthesia in hemodynamic parameters (blood pressure and heart rate) in both groups. The recovery time was shorter in propofol group compared with sevoflurane group. The time to obeying commands in propofol group was 5.8 min and 7.6 min in sevoflurane group. Postoperative nausea and vomiting were significantly more common in sevoflurane group (3 patients) than in propofol group (no one patient). Propofol group spent shorter time (92.3 min) in postoperative ward than sevoflurane group (103.2 min) before discharge home.

Conclusions:

Faster induction, recovery and absence of postoperative nausea and vomiting suggests that propofol has many advantages in ambulatory anaesthesia compared with sevoflurane.

References:

1. Gupta A. et al. *Anesth Analg* 2004;98:632-41
2. Moore J.K. et al. *Br J Anaesth* 2003;90:461-6

PHARMACODYNAMIC EFFECT OF CPB DURING PROPOFOL REMIFENTANIL TIVA FOR ADULT CARDIAC SURGERY AS REFLECTED BY CHANGES IN BIS

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Aim: To examine the clinical effect of cardiopulmonary bypass (CPB) on propofol - remifentanyl total intravenous anaesthesia (TIVA), using BIS, during adult cardiac surgery.

Methods: Ten adult patients for elective cardiac surgery under CPB were anaesthetised using propofol target controlled infusion (TCI) (target 1 mcg) and remifentanyl 1 µg/kg over 1 minute, followed by remifentanyl 0.2 – 0.5µg/kg/minute infusion. BIS was maintained between 40 and 55. Rescue hypnosis was administered based on BIS and clinical judgement.

During CPB, the propofol and remifentanyl infusions were continued. BIS readings were averaged and recorded every 5 minutes.

Results: BIS remained within the target range in all patients on instituting CPB.

Conclusion: The bispectral index is useful as a pharmacodynamic measure of the effect of anaesthetic agents on the central nervous system [1,2, 3]. Our observations demonstrate clinically that during a balanced TIVA with propofol (TCI) and remifentanyl, adequate anaesthesia is maintained during CPB, without need for change in the administration of remifentanyl and propofol, or additional hypnotic or analgesic supplements, and fits with the kinetics described earlier[4].

References:

1. Sebel PS, et al. *Anesth Analg* 1997; 84: 891-899
2. Struys M, et al. *Acta Anaesthesiol Scand* 1998; 42: 628-636
3. Molhoff T, et al. *BJA* 87 (5): 718-26 (2001)
4. Luis G. Michelsen, et al. *Anesth Analg* 2001;93:1100–5

ANAESTHETIC SERVICES IN SUB-SAHARA AFRICA

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Background: The state of anaesthesia services continues to be of great concern on the entire African continent and particularly so in sub-Saharan Africa. This is despite the fact that this region of the world is home to about 80% of the world's maladies that eventually surgical/anaesthetic intervention. The glaring high poverty levels experienced compounded by other priority health issues such as the HIV/AIDS crisis suffered by this region means that governments' focus and attention is elsewhere relegating anaesthesia almost to the garbage bin.

Methods: The author undertook an on the spot nationwide audit of anaesthetic services/facilities in

Zambia and a few surrounding nations with particular focus on the public health institutions.

Results: In all but one of the facilities visited, the state of anaesthetic services i.e. equipment and personnel needed much to be desired.

Conclusion: 90% of all the facilities visited lacked modern anaesthesia equipment. In some cases the situation was so grim that even basic intravenous requirements were unavailable. Further, manpower was either inadequate, under-qualified or almost non-existent. There is urgent need for concerned governments as well as the international community to urgently mainstream issues relating to anaesthesia practice in general and to intravenous anaesthesia more specifically

AWAKE INTUBATION USING TCI OF DEXMEDETOMIDINE REQUIRE A HIGH TARGET PLASMA CONCENTRATION

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We experienced 5 cases of awake intubation with dexmedetomidine using much higher target plasma concentration (TPC) than clinical dose. We evaluated intubation conditions and hemodynamics in these cases. Five patients (61-84 years old) with predicted difficult airway or risk for aspiration underwent awake intubation with dexmedetomidine using target-controlled infusion. TPC of dexmedetomidine was increased stepwise until that Ramsay sedation score reached 5 and pharyngeal reflex was preserved. An endotracheal tube was inserted when the patient did not show discomfort at the laryngoscope. Mean TPC of dexmedetomidine at the completion of tracheal intubation was 3.97 ng/ml (range, 2.10- 5.95 ng/ml), which is higher than that used clinically. Blood pressure increased in three cases and decreased in one case, all of which needed pharmacological intervention. Mean duration of intubation was 31 min. Spontaneous respiration was preserved and decrease in pulse oxygen saturation did not occur. Intubation conditions were good in four cases but poor in one case in which movement of limbs was vigorous and coughing was sustained for more than 10 sec. Vocal cord movement in laryngoscope and laryngeal reflex after tracheal intubation were preserved. Hemodynamic change after tracheal intubation was small, less than 15% in all cases.

The method using a high TPC of dexmedetomidine may be useful for awake intubation in patients with a risk for aspiration because respiration and vocal cord movement are adequately preserved despite elimination of patients'

discomfort. Further study is needed to evaluate the clinical usefulness of this method.

DEVELOPMENT OF ONLINE SIMULATION SOFTWARE OF IV ANESTHETICS IN THE ERA OF ELECTRIC ANESTHESIA RECORDING SYSTEM

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The simulation of IV anesthetics is a powerful tool for TIVA. Since many pumps incorporate the RS232C ports, the information of the infusion rate and total infused volume can be used for real time on-line simulation. Such software includes the legendary Stanpump (DOS) and our PropofolFMon (under Mac OS).

Recently, the Electric Anesthesia Recording System (EARS) have occupied the digital ports of pumps. As one RS232C port can communicate with one device but most EARS do not provide IV anesthetics simulation, we have lost the advantage of the on-line simulation in aid of TIVA.

To cope with this problem, the authors have developed the compact amplifier box (MonBox), which is inter-positioned between the pumps and EARS. MonBox enable us to peep serial communications between devices. It consists of an amplifier to buffer the transmitted digital data by using RS232 level converter Maxim 232 chip, USA, at the cost around 20 Euro. Self-powered design makes AC power adapter free.

Updated MonBox savy PropofolFMon (version 3.5) is developed by MacBook Pro with FutureBASIC 4, Staz software USA, under Mac OS-X. This software works under Mac OS 9 and Mac OS-X, which will be freely downloadable from homepage1.nifty.com/m_Nakao.

Supported pumps include TE-371, 332, 312, 525x, 171, 161 (Terumo), Graseby 3400/3500 (Smiths Medical), Ivac P-6002 TIVA (Alaris), AS-50 (Baxter), CoopDech CSP-100 (Daiken), S-1235 (Atom).

This is useful technique for the management of TIVA in EARS era.

THE EFFECT OF PROPOFOL ON THE SIGMA 1 RECEPTOR

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The sigma-1 receptor regulates the IP3 receptor function and is functionally linked with psychotomimetic effects of various drugs, cognition, and pain modulation. A sigma-1 receptor agonist enhances bradykine-induced intracellular Ca²⁺ concentration ([Ca²⁺]_i) increase and induces c-Fos expression in the posterior cingulate and retrosplenial cortices (PC/RS), which is a reliable marker of its psychotomimetic effects.

First, using wister rat brains, (+)[3H]SKF-10,047, a selective sigma-1 receptor agonist, was displaced by propofol, dexmedetomidine, droperidol, and thiopental. Second, Fura-2 loaded NG-108 cells were incubated with vehicle, 100 nM (+)pentazocine, a selective sigma-1 receptor agonist, 1, 10, or 100 μM propofol and then its fluorescence was observed after stimulating by 1 μM bradykinine. Third, male ICR mice were randomly assigned to 2 groups: The mice received Intrafat® or propofol intraperitoneally (ip), followed by pentazocine ip. Brain slices were prepared and Fos-like immunoreactivity was detected using immunohistochemical method.

Propofol, droperidol, and dexmedetomidine displaced (+)[3H]SKF-10,047 binding in a concentration-dependent manner with Ki50s of 10.2 ± 0.6, 0.17 ± 0.03, 5.73 ± 1.2 μM, respectively. Thiopental sodium was practically ineffective. Propofol produced a significant reduction in the Bmax but did not affect the Kd. (+) Pentazocine significantly enhanced bradykine-induced [Ca²⁺]_i increases, but propofol did not affect it. Pentazocine induced marked c-Fos expression in the PC/RS, which was significantly reduced by propofol.

These results suggest that propofol may be a sigma-1 receptor antagonist, and imply that various effects of propofol on the brain are mediated, at least partly, through the sigma-1 receptor.

EVALUATION OF SITE OF DRUG TOXICITY AFTER PROPOFOL INFUSION IN DOGS

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Introduction: We evaluated the time course of hemodynamic depression after propofol induction in dogs, to investigate contribution of propofol plasma (Cp) and effect site (Ce) concentration.

Materials and Methods: Sixteen adult Mongrel dogs undergoing elective surgery were sedated with

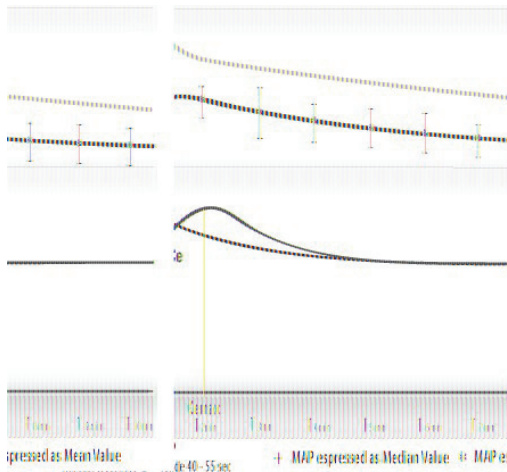
acepromazine (0,02 mgKg⁻¹) and morphine (0,15 mgKg⁻¹), then the dorsal pedal artery was cannulated and blood pressure monitored. Anaesthesia was induced with propofol (4,5 mgKg⁻¹ over 30 sec) and data were recorded every 10s for ten minutes via a serial interface. Dogs were intubated after 120 (+/- 6). A propofol effect site (ES) TCI was started 4 min after induction, being 4 mcg ml⁻¹ the predicted ES concentration. Cp and Ce time course were predicted using dogs PK(1) and PD(2). The ten minutes nadir of the mean arterial pressure (Map) was defined as TminMap. Data were analyzed with GraphPad.

Results: C_pmax (5,61 µgml⁻¹), at 31s after starting the infusion; C_emax and TminMap 119 sec and 45 (40-55) sec respectively. TminMap was 72 (+/- 6,5) mmHg.

Conclusions: In dogs Propofol TminMap is C_pmax related, suggesting the plasma is the site of drug toxicity

References:

1. Beths T, et al.(2001) Vet. Rec. 148, 198-203
2. Rabozzi R.et Novello L(2007) Proc. AVA Spring Conference, Paris



TWO CASES OF TRACHEAL DUMON STENT INSERTION USING HIGH DOSES OF DEXMEDETOMIDINE

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Aims:

We report two cases of general anesthesia with spontaneous breathing maintained using high doses of dexmedetomidine (DEX).

Methods and Results:

Case 1: A 42-year-old male with respiratory difficulty due to tracheal stenosis caused by multiple tracheal intubations and tracheotomies. Dumon stent placement was scheduled. Anesthesia was induced with 6 mcg/kg/h DEX for 10 minutes, and increased to 15 mcg/kg/h until loss of consciousness. Sedation was maintained with 9.4 to 15 mcg/kg/h DEX using bispectral index values. Fentanyl was given to prevent body movement. Spontaneous breathing was maintained throughout surgery, and consciousness returned within 3 hours.

Case 2: A 59-year-old male on long-term artificial respiration due to cardiac infarction requested management under spontaneous breathing. Anesthesia was induced with 12 mcg/kg/h DEX, and sleep was initiated within 15 minutes. Sedation was maintained with 3.5 to 10 mcg/kg/h DEX. Fentanyl was also required. Surgery took 1.5 hours, but spontaneous breathing was maintained with stable hemodynamics. Consciousness returned 3 hours later.

Discussions: Because hypoxemia due to apnea is problematic, it is desirable to maintain spontaneous breathing. Accordingly, we selected DEX, resulting in sufficient sedation with stable hemodynamics. Fentanyl was, however, required to prevent body movement, regardless of the high DEX dose. Fentanyl can cause respiratory depression, which requires close attention.

Conclusions: We describe two cases of tracheal stent placement using high doses of DEX. DEX enabled sedation during surgery while preserving spontaneous breathing. Anesthesia induction and awakening take time, and the choice of anesthesia should take this time requirement into consideration.

FEASIBILITY AND SAFETY OF INTRAOPERATIVE CONTINUOUS MONITORING OF CORTICO-SPINAL PATHWAYS DURING FRONTAL RESECTION FOR DRUG-RESISTANT NON-TUMORAL EPILEPSY UNDER TIVA

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The possibility to define the central sulcus is of great help in the identification of the motor cortex, but injuries to the motor pathways may occur subcortically. Therefore, continuous monitoring of MEPs is advisable.

Methods:

Three cases of frontal non-tumoral epilepsy were submitted to the resection of the epileptic focus. Anesthesia was induced with a loading dose of remifentanyl 3-4 ng/ml (Minto), followed after 5-8 min by propofol 5.5 µg/ml (Schnider). Anesthesia was maintained with remifentanyl 5-6 ng/ml and propofol in a range between 2.5 and 3.0 µg/ml. The central sulcus was identified using the somatosensory phase reversal technique. The motor cortex was mapped and the cortico-spinal tracts continuously monitored. Motor potentials were evoked using short trains of 3-5 stimuli, 0.5ms, ISI 4ms, up to 20mA, 0.5 trains/sec. The motor responses were recorded from muscles of the upper and lower extremities.

Results:

The mapping procedure lasted 5-5-9 min; the continuous monitoring lasted 90-63-54 min respectively. In all the cases, central sulcus identification was possible through the N20-P20 phase reversal. Continuous motor monitoring was performed in all the patients; no change in muscle responses was detected throughout the surgery. No motor deficit was present postoperatively. No complications were observed, particularly no intra or postoperative seizures.

Conclusions:

Our technique is feasible under general anesthesia, is reliable and safe in epileptic patients. No intra or perioperative seizures occurred with the short train high frequency technique. TIVA not only allows the cortical mapping in these epileptic patients, but allows the continuous intraoperative monitoring too.

FAST, ADVANCED, SAFE AND TOTAL INTRAVENOUS ANESTHESIA (FASTIVA) FOR MAJOR UROLOGICAL SURGERY (RADICAL PROSTATECTOMY)

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The synthesis of remifentanyl and muscle relaxants like cis-atracurium has facilitated the use TIVA made comparable this anesthesiological technique to the more diffused technique with halogenates, in relation to postoperative recovery and awakesness timings. One of the relevant and frequent problems with the use of remifentanyl is the control of immediate postoperative pain and the prevention of opioid deprivation syndrome. Use of opioids like morphine or fentanyl before the end of the surgical procedure was proposed for these inconveniences with consequent loss of advantages due to rapid metabolism of remifentanyl.

Utilization of BIS has permitted decreased use of hypnotics and decreased the time of postoperative awakesness. On the basis of these considerations we have developed an anesthesiological technique with multimodal approach.

40 adult patients (ASA II-III), underwent radical prostatectomy with the duration of about two hours under following anesthesiological procedure. All patients were monitorized and were treated with paracetamol, desametasone and ranitidine and were premedicated with atropine and midazolam.

An epidural catheter was positioned at level of T12-L1 and 100mg of levobupivacaine 7.5% was administered, followed by the induction of general anesthesia with sufentanyl 0.3ug/kg, cis-atracurium 0.15mg/kg and propofol 2.5mg/kg. TIVA was maintained with propofol 4-5ug/kg/min., remifentanyl 0.15ug/kg/min., cis-atracurium 1-2ug/kg/min. and continuous epidural infusion of levobupivacaine 0.2% and mechanical ventilation with O2/air 50%/50%.

Patients were monitored with MABP, SatO2, EtCo2 and BIS. Recovery and discharge timings of the patient from operating room were extremely satisfactory and we consider this procedure useful for the major urological surgery.

HOW TO CORRECT MINTO'S PHARMACOKINETIC SET IN MORBIDLY OBESE PATIENTS: THE "FICTITIOUS HEIGHT" IN WOMEN (II)

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Background: In the previous abstract we explained how to correct Minto's pharmacokinetic set (PK) in morbidly obese female patients according to the "fictitious height". In this abstract this correction will be tested by means of a simple computer simulation.

Methods: We focused on a 40 year-old obese female patient, weighing 190 kg, 1.65 m tall and a non-obese control patient, aged 40 years, weighing 65 kg, 1.65 m tall, during a simulated Target Controlled administration of remifentanyl of 120 minutes set at 2 ng/ml. In the obese patient, the weight was corrected according to the mathematically derived formula presented previously.

Results:

Simulations for the morbidly obese patient (unadjusted PK set), control patient and morbidly obese patient (adjusted PK set) are summarized in Table 1.

Conclusions:

Changing the input height according to the “fictitious height” corrects Minto’s PK set in morbidly obese female patients.

Patients' Demographic Features, Minto's Pharmacokinetic Parameters and Remifentanyl Consumption			
Variable	Obese Patient	Matched Control	Obese (h corrected)
Sex	F	F	F
Age (yr)	40	40	40
Height (m)	1.65	1.65	1.99 (h _q)
Weight (kg)	190	65	190
LBM (kg)	7.05	46.58	68.38
BMI (kg/m ²)	69.8	23.9	48.0
V ₁ (l)	1.6479	4.4939	6.0637
V ₂ (l)	4.6414	8.9106	11.2650
V ₃ (l)	5.42	5.42	5.42
K ₁₀ (min ⁻¹)	0.5950	0.5950	0.5950
K ₁₂ (min ⁻¹)	1.0221	0.5428	0.4709
K ₂₁ (min ⁻¹)	1.2440	0.4562	0.3381
K ₁₃ (min ⁻¹)	0.4416	0.2301	0.1820
K ₃₁ (min ⁻¹)	0.0461	0.0169	0.0125
Cl ₁ (l/min)	0.0140	0.0140	0.0140
Cl ₁ (l/min)	1.6842	2.4392	2.8556
Remi120 (mcg)	424	620	728

Table 1: Patients' demographic features, Minto's pharmacokinetic parameters and remifentanyl consumption of the obese vs non-obese patient for a hypothetical infusion of 120 minutes. The two central columns represent the comparative simulation when no correction is used in the obese patient. The right column shows what happens when the height of the morbidly obese patient has been corrected according to the “fictitious height”. It is evident that this corrects the pharmacokinetic set and allows its use despite the fact that it incorporates wrong equations for the calculation of LBM values.

TARGET CONTROLLED INFUSION OF REMIFENTANIL: BEWARE WHEN USING IT IN MORBIDLY OBESE PATIENTS

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Background:

The pharmacokinetics of remifentanyl have been extensively studied both in non-obese and in obese patients. This led to the possibility to administer remifentanyl in a target-controlled fashion. Is this way of administration reliable even in morbidly obese patients?

Methods:

We carried out a simple computer simulation of a Target Controlled Infusion (TCI) of remifentanyl. We focused on a 40 year-old obese female patient, weighing 205 kg, 1.70 m tall and a non-obese control patient, aged 40 years, weighing 55 kg, 1.70 m tall, during Target Controlled administration of remifentanyl of 120 minutes set at 2 ng/ml.

Results:

The effects of this simulation on some parameters of the pharmacokinetic set of Minto, remifentanyl consumption and patients' demographic features are listed. Lean Body Mass (LBM) appears to be only 4.14 kg in the obese patient, compared to 43.36 kg in the non-obese patient. The use of this commercially available pharmacokinetic set would cause a 66 % decrease in calculated V₁, a 49 % decrease in V₂ and a 32 % decrease in Cl₁. In this way, over 120 minutes we would administer a total amount of 604 µg remifentanyl to the non-obese patient, whereas only 410 µg (-32 %) would be administered to a patient weighing almost four times as much. This would be clinically unacceptable and would cause a lack of predictive performance of the system.

Conclusions:

These results indicate that this model is unreliable in morbidly obese patients and cannot be used at present.

TARGET-CONTROLLED INFUSION FOR REMIFENTANIL IN VASCULAR PATIENTS FOR CAROTID SURGERY IMPROVES HEMODYNAMICS AND DECREASES REMIFENTANIL REQUIREMENTS

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Remifentanyl, a potent ultra-short-acting opioid, permits rapid emergence and sedation modulation. However, remifentanyl is expensive and may have detrimental effects on hemodynamics and respiratory function. TCI permits adapting infusion to pharmacokinetic models. In this prospective randomized study, we compared intra- and postoperative hemodynamics, remifentanyl requirement during anesthesia, in patients scheduled for carotid endarterectomy. Twenty-two patients were enrolled after the randomization, divided in two groups (TIVA vs TCI). After remifentanyl start infusion, was performed deep and superficial cervical block (Ropivacaine 7.5%). Eleven received TIVA [(0.05-0.1 mcg/kg/min with step of 0.05 mcg/kg/min; eleven received TCI (Minto model, Alaris PK), with an effect-site concentration at 1-2 ng/mL. All patients received 50% mixture of Air/O₂(2). Hemodynamic variables were recorded each minute. Data were analyzed by using unpaired t-tests. TIVA was significantly associated with more frequent episodes of intraoperative hypotension (16 versus 6, P < 0.001). TCI led to a significantly smaller

requirement of remifentanyl (700 +/- 290 versus 1390 +/- 555 micro g, P < 0.001). This study demonstrated that TCI group results in less hypotensive episodes, fewer episodes of tachycardia/hypertension, with a decrease in remifentanyl requirement. Recommendations to prefer TCI for remifentanyl administration during carotid endarterectomy may be justified. This may be related to a smaller requirement of this drug when using target-controlled infusion, as well as a smooth mode of administration.

- De Castro V et al. *Anesth Analg.* 2003 Jan;96(1):33-8
- Derrode N. et al. *Br J Anaesth.* 2003 Dec;91(6):842-9
- Godet G. et al. *Br J Anaesth.* 2004 Mar;92(3):329-34

COMPARISON BETWEEN TIVA WITH PROPOFOL-REMIFENTANIL VS SEVOFLURANE-FENTANYL ANAESTHESIA IN MORBID OBESITY PATIENTS

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Background: The choice of anesthetic technique for general anesthesia in morbidly obese patients remains controversial in order to minimize the risks of aspirative pneumonitis, hemodynamic instability and delay in recovery. The ideal anesthesia should provide a smooth and quick induction, allowing rapid airway control, hemodynamic stability, rapid emergence.

Goals: We compare vital parameters and recovery performing TIVA and sevoflurane-fentanyl anaesthesia in morbid obesity patients candidate to removal of bioenteric intragastric balloon.

Settings: University Hospital

Methods: 28 morbidly obese patients, scheduled for elective bariatric surgery were allocated to 2 groups: T (TIVA group, n°13) and S (sevoflurane group, n°15). In Group T, anesthesia was performed with propofol remifentanyl. In Group S, anesthesia induction was achieved by sevoflurane with single breath technique, and maintenance with 1-2% volume sevoflurane and fentanyl. Nonparametric Friedman test was used for data analysis; p < 0.05 was considered statistically significant. Time to loss of consciousness, tracheal intubation, perianesthetic physiological parameters and complications, incidence of awareness, recovery times, postoperative analgesia were evaluated with Postanesthesia Discharge Scoring System (PADSS).

Results: See table

Conclusion: Our preliminary data showed that both techniques results effective, secure and predictable without statistic relevant differences between the two techniques for the anesthetic management of morbidly obese patients.

loss of consciousness p-value tracheal intubation p-value

GrpT	Grp S		GrpT	Grp S
1.7±0.6	1.9±0.4	<0,100	4.0±0.8	3.4±0.3
<0,180				

Timing after estubation PADSS

	GroupT	Group S
5'	5,94±0,76	17±0,8<0,620
15'	8,77±0,88	03±0,5<0,749
30'	9,62±0,39	54±0,2<0,953

Reference:

- Marshall SI, Chung F. *Anesth Analg.* 1999;88;508-17

DESIGN OF A CLOSED LOOP CONTROLLER FOR INTRAVENOUS ANESTHESIA WITH PROPOFOL

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Background:

A modelling study and the design of a closed-loop control system for total intravenous anaesthesia using propofol were done. The controlled variable considered was the Bispectral Index (BIS).

Methods and Results:

The first aim was to obtain a mathematical model of the system represented by the patient undergoing an anesthetic process with propofol by means of system identification techniques. A parametric ARX model estimation was performed with a group of five patients of different weight, sex and age undergoing major surgery with propofol. A segment of the input data was used to obtain the model and the remaining data set of the same patient for validation. The results showed that the order of the adequate model varies between 15 and 20 depending on the patient and the phase of the surgery.

The model obtained was validated with data sets of other patients and satisfactory results were obtained.

A software tool was developed to perform manual and automatic control of the infusion process. At this moment there are two controllers implemented: PID control and fuzzy controller. The PID control computes the dose of drug to be applied using information of the error signal. Three variables were considered as inputs to the fuzzy module: the BIS error and its derivative and the current BIS.

Conclusions:

First results obtained in patients with the PID strategy attest the efficiency of the scheme proposed. The controller is able to regulate the BIS index even in long duration operations with mean offsets around 10%.

CLOSED-LOOP CONTROL OF PROPOFOL INFUSION USING THE BIS: PRELIMINARY RESULTS

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Background: Our group developed a closed-loop control system for propofol based on a proportional-differential algorithm guided by the Bispectral Index (BIS). Fine tuning of the PID was obtained after a pilot study of 25 patients. The aim of this study was to evaluate the performance of this software during stable phases of surgery. We present our preliminary results after adjusting the values of the PID.

Methods: After Institutional approval, 7 patients, ASA I-II, scheduled to undergo elective abdominal surgery were included. The goal was to make a manual induction with propofol and remifentanyl and maintain a BIS target of 50 during the maintenance of anesthesia. Remifentanyl infusion was adjusted manually and rocuronium was administered in bolus as needed. We recorded hemodynamic changes and indirect signs of intraoperative awareness.

Results: Closed-loop control was able to provide maintenance of anesthesia for all patients, there were not dangerous oscillations. There were not registered unwanted somatic events, intraoperative awareness or hemodynamic instability.

The MDPE = -1.2803. MDAPE = 9.9012. WOBBLE = 9.6133. The OFFSET = -0.5723. Time of control was 79 (33-185) min.

Conclusion: Our preliminary results with a short number of cases provided adequate anaesthesia in all patients. Automatic control of consciousness with an infusion of propofol using the BIS as the control variable with an original PID controller was clinically feasible.

BALANCED ANAESTHESIA VS TIVA: INCIDENCE OF PONV AND PAS

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Background: To evaluate the incidence of postoperative nausea and vomiting (PONV) and postanesthetic shivering (PAS) in 40 patients submitted to gynaecologic laparoscopy, comparing balanced anaesthesia to total intravenous anaesthesia (TIVA).

Patients and Methods: Patients (ASA I-II) were randomly allocated to receive either balanced anaesthesia, using propofol, fentanyl and sevoflurane (Group A n = 20) or TIVA, using propofol and remifentanyl (Group B n = 20). We used ketorolac and tramadol for postoperative analgesia in both groups. The incidence of PONV was evaluated for 12 hours postoperatively. The incidence of PAS was evaluated, recording the temperature, measured after induction of anesthesia (T0), 15 min (T1), 30 min (T2), 60 min (T3) and 120 min (T4) after reaching the ward.

Results: Group B suffered less PONV, with a reduced requirement of antiemetic medications. The incidence of PONV was 55% (11/20) in Group A and 35% (7/20) in Group B. In the TIVA Group, 60% (12/20) patients suffered from PAS, compared with 20% (4/20) in the balanced anaesthesia Group.

Conclusions: In our study the incidence of PONV was higher in the Group A, whereas the incidence of PAS was higher in the Group B, even if temperature showed no significant difference between the two Groups. PONV and PAS are unpleasant complications after surgery, influenced by many variables and the anaesthetic management may have an effect on them.

Reference: White H, Black RJ, Jones M, et al. "Randomized comparison of two anti-emetic strategies in high-risk patients undergoing day-case gynaecological surgery". *Br J Anaesth.* 2007 Apr;98(4):470-6.

PULSE OXIMETRY - CONTROLLED INFUSION SYSTEM FOR CONSCIOUS SEDATION

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Introduction: Remifentanyl could produce respiratory depression. Anesthesiologist usually should modify the infusion rates or administer supplementary oxygen to avoid hypoxia. An automatic infusion system where pulse oximetry controls the infusion rate, was developed. The communication between the pump and the pulse oximetry, it is based in the frequencial analysis of the auditive pitch of the pulse oximetry beep. Pulse oximeters emit beeps with modulated frequency proportional to oxygen saturation. In the Nellcor mode the beep has a pitch of 662 MHz when O₂ Sat is 100%; this frequency is reduced 5 Hz at each 1% decrement in O₂ Sat. The system analyzes the sound present in the room, identifies the monitor beep by frequency analysis, determines the frequency of the pitch and translates the value to percentage of transcutaneous oxygen saturation, modifying if necessary the infusion rate.

Objective: To assess feasibility of a device based in this technology to minimizing respiratory depression.

Patients and Methods: 25 patients ASA I – II, between 18- 65 y. scheduled for elective surgery under regional anesthesia. Conscious sedation will be accomplished by Remifentanyl to the desired level of sedation

Results: The system reduces remifentanyl infusion rate as expected, avoiding Sat O₂ below 90% and cutting automatically the infusion when reaches 90%.

Conclusions: The frequencial analysis of the Sat O₂ beep, could be a good way to communicate a pump without wires and special connectors. A Pulsoxymetre controlled infusion system could avoid respiratory depression without modify the sedation quality.

MONITORING NEUROMUSCULAR FUNCTION WITH THE BLOOD PRESSURE CUFF

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Background: A new method of monitoring neuromuscular blockade based on a modified block pressure cuff that incorporates stimulating electrodes was compared with mechanomyography (MMG) ('gold standard').

Methods: 60 adults (ASA I–II) underwent neuromuscular blockade monitoring on the contralateral arms and on the same arm using the new cuff method and MMG. Only train-of-four (TOF) ratios > 0.1 and T1 heights > 0 were studied. Supramaximal stimulation was also assessed. A device based on a PC with an analogue-to-digital conversion card was used to control

and synchronize MMG and the cuff method. The agreement between both methods was assessed using the statistical method of Bland and Altman.

Results: When TOF ratios were > 0.7, the bias between the two methods was 0.04 with the limits of agreement ranging from 0.21 to 0.12 (95% CI 0.06 to 0.02). The T1 > 0 heights bias was 0.01 with the limits of agreement ranging from 0.26 to 0.24 (95% CI 0.02 to 0.003). The sensitivity of the cuff method was 88%, with a specificity of 85% and an accuracy of 86%.

Conclusion: This study indicates that the cuff method could be useful to monitor neuromuscular blockade for daily clinical use. The new cuff method is easy and simple to use. More studies in a larger number of patients will be necessary to confirm these favourable results.

Key Words: Neuromuscular blockade; inflatable cuff; mechanomyography; monitoring; intra-operative instrumentation; anaesthesia, general

ANESTHESIA FOR A PREGNANT WOMAN UNDERGOING AN URGENT CRANIOTOMY

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Background: Information regarding the safety of anesthesia during pregnancy is limited. There is strong aversion to drugs used for procedures being performed during pregnancy. This is because anesthetic management involves two separate patients (mother and fetus) and the physiology specific to pregnancy. Some reasons that make anesthesia for pregnant women such a challenge. The objective is to present an example of a pregnant patient submitted to craniotomy under TIVA.

Case Report: 37 year old woman, at 30 weeks of gestation, who was diagnosed a massive frontal meningioma requiring urgent craniotomy. Prophylactic use of tocolytic agents were preoperatively discuss with the obstetrician. Initial monitoring consisted of noninvasive/invasive blood pressure, continue ECG, oxicapnography and continuous cardiotocography (CTG).

Left uterine displacement was maintained preoperatively. Anesthesia was induced with propofol in controlled target infusion (3 µg/mL) and continuous remifentanyl (1 µg/kg in bolus, 0.2 µg/kg/min for maintenance). Rocuronium (40 mg) was administered for muscle relaxation. Anesthesia was maintained with the infusions mentioned, in addition to rocuronium complementation. Fetus was continuously monitored with CTG accomplished and analyzed by the

obstetrician. Hyperventilation was avoided once it reduces maternal cardiac output and decreases oxygen release to the fetus. Propofol and remifentanyl infusion pumps were turned off by the end of the procedure (slow reversal of relaxants was performed to prevent uterine contraction) and patient woke up 12 minutes later, without pain and hemodynamically stable.

Conclusions: TIVA has provided hemodynamic stability for mother and fetus (no signs of distress) and preterm labor during peroperative period was avoided.

SEDATIVE PROPERTIES OF SMALL-DOSE OF DEXMEDETOMIDINE IS QUALITATIVELY DIFFERENT FROM PROPOFOL INDUCED SEDATION

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Objective:

Although dexmedetomidine (DEX) could achieve similar bispectral index (BIS) values with propofol induced sedation, sedative properties from both drugs are completely different. Accordingly we tested our hypothesis we can distinguish DEX sedation from the propofol sedation even at similar BIS values.

Methods:

9 patients (ASA 1-2, 20-75 yrs) scheduled for spinal anesthesia were randomly and double-blindly assigned to receive either DEX (D group, N=5) or propofol (P group, N=4). We measured the Observer's Assessment of Alertness/ Sedation Scale (OAAS) at BIS 70 and at 50, respiratory rate (RR), blood pressure (BP), heart rate (HR), SpO₂ and the changes of BIS values during calling patients' name in normal tone.

Results:

Demographic and morphometric data were similar in the groups. MBP was significantly less at BIS 50 and 70 in the P group vs. preoperative values but not in D group. On the other hand, HR was significantly less at both BIS 50 and 70 in D group compared with preoperative values, but not in the P group. There was no significant change in RR, but one case in P group was necessary to assist ventilation at BIS 50. OAAS in P group was significantly lower than D group at both BIS 50 and 70. The changes of BIS values during calling patients' name were significantly increased at BIS 50 and 70, the degree of increase in the D group was significantly larger.

Conclusion:

We could distinguish the DEX or propofol induced sedation even during the same BIS values.

CROSS-CLAMPING OF THE DESCENDING THORACIC AORTA LEADS TO THE ASYMMETRICAL DISTRIBUTION OF PROPOFOL DURING CARDIOPULMONARY BYPASS SURGERY

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We investigated the effect of cross-clamping the descending thoracic aorta (CcDTA) on the plasma propofol concentration (C_p) centrally and distally, including the pulmonary artery and the inlet of cardiopulmonary bypass (CPB).

Methods:

The Bispectral Index (BIS) was recorded during CcDTA in six patients undergoing thoracic aortic surgery using total intravenous anesthesia with propofol. The calculated C_p was maintained at 3 µg ml⁻¹ using the target controlled infusion technique. The C_p was measured in blood samples drawn from the right radial artery, left dorsalis pedis artery, pulmonary artery, and long venous CPB cannula.

Results:

Five minutes after initiating CcDTA, the BIS decreased significantly in all cases. The BIS kept decreasing, along with the high propofol concentration in the upper limb. During CcDTA, the C_p of samples from the radial and pulmonary arteries was significantly higher than those from the dorsalis pedis artery and venous cannula ($p < 0.05$). The C_p in samples from the pulmonary artery was two to three times higher than in samples from the venous duct.

Conclusions:

Kakinohana et al. (Anesthesiology 2006; 104: 939-43) reported that the C_p increased and the BIS decreased rapidly after CcDTA during propofol anesthesia. Our results were consistent with theirs and confirmed the presence of a C_p difference between the pulmonary artery and venous CPB duct. The results indicate that almost all of the blood returning from the superior vena cava enters the pulmonary circulation directly, without mixing with blood from the inferior vena cava.

IDENTIFICATION OF BETTER PHARMACOKINETIC PARAMETERS FOR PROPOFOL INFUSION TO PREDICT BISPECTRAL INDEX RESPONSE

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Pharmacokinetic (PK)-pharmacodynamic (PD) models are widely applied to predict the response of the Bispectral Index (BIS) to propofol administration. The conventional PK parameters, such as those used in the Diprifusor, are obtained from intermittent measurements of blood propofol concentrations, but they are not necessarily suitable for the prediction of the BIS response. To improve accuracy in BIS prediction, we have identified better PK parameters than those used in the Diprifusor.

Methods:

Propofol infusion rate and BIS values were recorded every 10 sec in 78 patients (ASA PS I-II, 18-80 yr.) undergoing short-stay surgery. Propofol was administered continuously following an initial 2 mg/kg bolus. PK parameters were calculated using the MATLAB Optimization Toolbox (Math Works), through the following procedure:

- 1) PK parameters used in the Diprifusor were set as the initial ones.
- 2) Taking a time delay into account, PD parameters of each patient were identified, so as to minimize root-mean-square error (RMSE) between the output of the PK-PD model (predicted BIS values) and the actually measured BIS values.
- 3) Step 2) was iterated. The optimal PK parameters that minimize root-mean-square of RMSEs among all patients were identified.

Results:

The identified PK parameters were $k_{10}=0.229 \text{ min}^{-1}$, $k_{12}=0.356 \text{ min}^{-1}$, $k_{13}=0.165 \text{ min}^{-1}$, $k_{21}=0.266 \text{ min}^{-1}$, $k_{31}=0.137 \text{ min}^{-1}$ and $ke_0=0.516 \text{ min}^{-1}$. The RMSEs using the parameters (6.98 [1.84], mean [SD]) were smaller than those using the Diprifusor's ones (7.50 [1.95]) ($p<0.05$, Wilcoxon rank-sum test).

Conclusion:

PK parameters obtained are better than those used in the Diprifusor for prediction of BIS response to propofol infusion.

CHARACTERIZATION OF PROPOFOL PHARMACODYNAMICS WITH THE CSI USING THE MARSH AND THE SCHNIDER PHARMACOKINETICS MODELS

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Background: The Cerebral State Index (Danmeter) is a new device to monitor depth of hypnosis based on a fuzzy logic analysis of the EEG. The aim of this study is to characterize the pharmacodynamics (PD) and ke_0 of propofol utilizing the CSI as the measured response.

Methods: After routine monitoring and CSI, eighteen volunteers, 21-45 yr, were sequentially assigned to receive either a bolus of propofol 1.8mg/kg (1200ml/hr) (Group B) or an infusion of 12mg/kg/hr until $CSI \leq 50$ (Group I). After spontaneous recovery to CSI basal values the same bolus dose administered to group B was now administered to group I and the same infusion scheme of group I was now given to group B. The study finished after spontaneous recovery of CSI following the second dose scheme. The CSI response was recorded every 1 second. The pharmacokinetic (PK) parameters from Marsh and Schnider were used to predict the plasma concentrations of propofol. The complete response curves of CSI were then used in a population PK-PD modeling analysis using a sigmoidal Emax model with NONMEM.

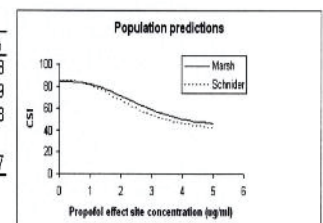
Results: The Ke_0 and PD parameters estimated for Schnider and Marsh PK models are shown in table. Figure shows the propofol C_e -CSI relation obtained with the population estimated parameters (table).

Conclusions: In this population the propofol C_e -CSI relationship applied to the Marsh and Schnider PK models was adequately characterized using the estimated ke_0 s and PD parameters.

References:

1. BJA 67:41-48, 1991
2. Anesthesiology 88:1170-82, 1998
3. Anesthesiology 105:28-36, 2006

	Marsh		Schnider	
	Typical value	CV%	Typical value	CV%
ED	84.40	13.00	84.80	13.78
EMAX	37.70	32.56	36.40	14.59
CS0 (ug/ml)	2.63	21.73	2.44	27.48
GAM	2.76		2.77	
KE0 (min ⁻¹)	0.67	60.60	0.26	63.17



TIVA AND HAEMORRHAGIC SHOCK

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The unawareness of pharmacological drug changes hypovolemic shock, has troubled anaesthetic management.(1) The aggressive fluid reanimation to recover body fluids, oxygenation and to protect vital organs has been, so far the focus of medical treatment. In 1978, a 10 year-term survey showed showing that the anesthetic induction was the first cause of death during hypovolemic shock(2).

Since hemodynamics is priority number one about reanimation, intraoperative awareness has shown an increased incidence in this group of patients (3) up to 43% (4) . Lately, the incorporation of EEG monitors (5), and PK-PD models for administration of anaesthesia have improved optimized the use of drugs in hypovolemic patients.

Our fair knowledge could be understood within the context of a high changing scenario with ethical restrictions for performing big clinical studies.

In 1960, Price (6), and then Weiskopf in 1985, both suggested that with normal body volume is reduced in 30%, we need to reduce thiopental doses in 40% and ketamine in 33%(7). Midazolam in the same condition prolongs its half life, has a decreased clearance, and shows a greater hypotensive effect.(8)

Some of the physiopathological changes which explain changes in pharmacology of inhaled drugs during hypovolemia are the increase of pulmonary shunt and the decrease of cardiac output. The equilibrating time of F_e/F_i is reduced, therefore overestimating blood concentration of drugs.

The intravenous drugs increase their blood concentration because of the fall in the heart performance and the subsequent vascular reaction. The decrease in hepatic clearance is associated with hypotension, hypothermia or acidosis. Hemodilution and hypothermia affect drug distribution. All these effects overestimate drug plasma concentration when using commercial pumps with PK-PD models.

Until now, comparing the studies with intravenous and inhalation drugs in hypovolemic shock is not possible because the methodology is totally different.

The increase of acute-phase reactive proteins affects the amount of free drug, specially those of basic character like alfentanil, by increasing its volume of distribution (Vd). The less available albumin increases the amount free drugs like Propofol (acids), by diminishing its Vd. Metabolic acidosis diminishes the ionizable drug distribution like muscle relaxants.

Survey models in animals, like rats, dogs or pigs, are not totally feasible to humans. Until now, these studies have not utilized animals during hypovolemic states greater than 65%. The pharmacodynamics evaluations have been done with different EEG analysis techniques, thus making comparison difficult. The resuscitation form could also affect the interpretation of the results.

Pharmacology of the Drugs in hemorrhagic Shock:

In surveys during hypovolemic shock, fentanyl (9) administrated in 40% of volemia bled out pigs, pharmacokinetics changes suggest a 50% less drug requirements. The decremental time isare also prolonged. Remifentanyl, in 65% of the volemia bled out pigs(10), results in a contraction of the V1 and clearance reduction, without prolonging the context sensitive half life. From a clinical point of view, we have to reduce Remifentanyl doses in about 40% to reach equal Cp.

Drugs like etomidate (11,12) show minimal PKPD variation. Propofol, however, has very different results. In animals (13,14) bled out up to 50% of the volemia, without reanimation, the systemic vascular resistances and heart rate HF goes up until a collapse point. The CO falls down and the Cp propofol increases progressively. In hemorrhage over 50% with cardiovascular collapse, the Cp increases 3.75 times. But after recovering volemia with 3:1 cristaloids or colloids, the Cp of propofol was similar to control., The pharmacodynamic analysis has shown an increase of sensitivity of the drug (15) during shock states and only partial recovery after volume reanimation (16).

The use of the EEG is probably highly indicated in these patients (18), but it is necessary to consider the effects of the acidosis, isquemia or drugs like ephedrine (19) on the EEG itself.

From pPreliminary data in war casualties patients indicate that the use of anesthesia in patients having hemorrhagic shock would reduce the intensity of the inflammatory response.

With the obtained data, probably the anaesthetic technique with remifentanyl in a 30% reduced doses, low doses of Ketamine, and propofol reduced around 30 to 70%, depending of the amount of the hypovolemic state, could be adequate to maintain this patient stable and without risk of awareness.

References:

1. Halford. *Anesthesiology* 1943; 4:67-69.
2. Harrison. *BJA* 1978, 50: 1041-1046.
3. Sandin. *Lancet* 2000; 355:707-711.
4. Bogetz. *Anesthesiology* 61:6-9. 1984.
5. Myles. *Lancet* 204;363:1757-1763.

6. Price. *Anesthesiology* 1960;21:40–45.
7. Weiskopf. *BJA* 57(10): 1022-5, 1985.
8. Adams. *Anesthesiology* 63(2):140-6, 1985.
9. Egan. *Anesthesiology* 91:156-66, 1999.
10. Jonhson. *Anesthesiology* 94:322-332, 2001.
11. De Paepe. *J Pharmacology Exp Ther* 1999;290:1048-53.
12. Johnson. *Anesth Analg* 96:1360-8, 2003.
13. De Paepel. *Anesthesiology* 2000; 93: 1482-90.
14. Kazama. *Anesthesiology*, 97:1156:61, 2002.
15. Johnson. *Anesthesiology* 99(2) 409-20, 2003.
16. Johnson. *Anesthesiology* 101:647-59, 2004.
17. Kurita. *Anesthesiology* 100(4) April 2004 pp 871-878.
18. Honan. *Anesthesiology* 97:1303-1305, 2002.
19. Takizawa. *EJA* 23:654-57, 2006.

SPEED OF INDUCTION AS A COVARIATE OF PROPOFOL PHARMACODYNAMICS WITH THE EEG CSM MONITOR

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Background:

In a previous abstract we characterized the global effect site concentration–CSI relation using both, a standard bolus dose and an infusion scheme of propofol using the Marsh and Schnider PK models. In this study we estimated the impact of the administration scheme in the dynamic profile of propofol effect measured with the CSI.

Methods:

Eighteen healthy volunteers were sequentially assigned to receive either a bolus of propofol 1.8 mg kg⁻¹ (1200 ml hr⁻¹) followed by an infusion 12 mg/kg/hr until CSI ≤ 50 (n=10) or first the infusion followed by a bolus dose (n=8). The CSI response was automatically recorded every 1 second. After each induction scheme spontaneous recovery of CSI to basal values was mandatory. The complete response curves of CSI were used in a population PK-PD modeling analysis using a sigmoidal Emax model with NONMEM. The impact of the administration scheme was evaluated introducing this variable as a covariate of the estimated parameters. The pharmacokinetic parameters published by Marsh and by Schnider were used to predict the

plasma concentrations of propofol during the study period.

Results:

The goodness of fit of both PK-PD models significantly improved (p<0.05) when the administration scheme was included as a covariate of the ke0 (Table 1).

Conclusions:

The dynamic profile of propofol evaluated with CSI was affected by the administration scheme.

1. Marsh. *Br J Anaesth* 67:41-48, 1991
2. Schnider. *Anesthesiology* 88:1170-82, 1998

Model	Bolus infusion CV%			
Marsh	Ke0 (min ⁻¹)	1,01	0,56	50
Schnider	Ke0 (min ⁻¹)	0,35	0,23	50

HEART RATE VARIABILITY AND BISPECTRAL INDEX DURING RECOVERY FROM ANESTHESIA: A COMPARISON OF TOTAL INTRAVENOUS ANESTHESIA AND BALANCED ANESTHESIA

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Aims:

We compared heart rate variability (HRV) and bispectral index (BIS) during recovery from anesthesia in patients receiving total intravenous anesthesia (TIVA: propofol / fentanyl or remifentanyl) and balanced anesthesia (BAL: sevoflurane / fentanyl or remifentanyl).

Methods:

Twenty patients (American Society of Anesthesiologists physical status I or II, aged 20–60 years) were randomly allocated into the TIVA group (fentanyl: n=5, remifentanyl: n=5) or BAL group (fentanyl: n=5, remifentanyl: n=5). Anesthesia was induced with fentanyl, propofol and vecuronium bromide, and tracheal intubation was performed in both groups, with an infusion of 4–8 mg/kg/hr propofol in the TIVA group

and inhalation of 0.5-1.5 minimum alveolar concentration (MAC) sevoflurane in the BAL group. HRV analysis was performed using the maximum entropy spectral analysis method (MemCalc method), and the low frequency (LF: 0.04-0.15 Hz), high frequency (HF: 0.15-0.4 Hz), LF / HF ratio, ultra short-term entropy and gradient value of the 1/f slope were measured. These indices were measured before induction of anesthesia (control value), and after induction, and during recovery from anesthesia.

Results:

Changes in all values differed between the two groups, and the relationship to the BIS value also showed different patterns during recovery from anesthesia.

Conclusions:

It was suggested that a combination of HRV and BIS measurements was useful for assessing the depth of anesthesia in both groups.

DEXMEDETOMIDINE BUT NOT PROPOFOL ENHANCES INOTROPIC ACTION OF DOBUTAMINE

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Background:

Dexmedetomidine (DEX) and Propofol (PF) are widely used for the sedation of critically ill patients who are receiving catecholamines for hemodynamic support. Thus, it is of clinical importance whether PF and DEX could alter catecholamine-induced inotropic response. This study was carried out to determine the effects of DEX and PF on dobutamine (DOB)-induced cardiovascular responses using anesthetized pigs.

Methods:

Pigs were anesthetized with chloralose and fentanyl, and were mechanically ventilated. After measurements of baseline hemodynamic data, the pigs were divided into three groups. Group D (n = 10) received DEX, 1 mg•kg⁻¹, as an initial loading dose followed by continuous infusion at a rate of 0.6 mg•kg⁻¹•h⁻¹. Group P (n = 10) received PF, 1 mg•kg⁻¹ as an initial dose followed by 3 mg•kg⁻¹•h⁻¹. Group C (n = 10) received vehicle. Then all groups received continuous IV infusion of DOB at incremental infusion rates (3, 5, 7, and 10 mg•kg⁻¹•min⁻¹) for 15 min at each rate, and measurements were made before and during DOB infusion.

Results: DEX significantly decreased heart rate (HR), mean aortic pressure (mAP), and cardiac output (CO). PF significantly decreased mAP, but had no effects on DOB-induced cardiovascular responses. On the other hand, DEX significantly enhanced DOB-induced increase in mAP without increase in HR. The DOB-induced increase in SV in group D was greater than that in group C.

Conclusions: DEX but not PF enhances DOB-induced blood pressure response, and this effect is mediated through increase in SV.

ASSOCIATION OF PROPOFOL AND REMIFENTANIL FOR TIVA/TCI IN MORBIDLY OBESE PATIENTS

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Background: The pharmacokinetics of propofol and remifentanyl have been extensively studied in non-obese individuals. This led to the possibility of administering both drugs in a target-controlled fashion. The feasibility of this system has been tested in non-obese patients, but few studies have been performed in the obese population.

Methods: 40 morbidly obese patients (ASA II-III, BMI 40-80, age 29-64 yrs) scheduled for bilio-intestinal bypass surgery were prospectively studied. Standard monitoring, including BIS Index, was used throughout the study. After awake nasotracheal intubation had been performed, anesthesia was induced with a propofol target concentration of 5 mcg/ml, which was subsequently adapted to maintain stable BIS values ranging between 40 and 60. Remifentanyl target concentration was adjusted to maintain heart rate and mean arterial blood pressure between ±10% of the basal values. Hemodynamic and respiratory parameters, as well as BIS Index values were recorded every 5 min and at specific times. Times to emergence and side effects were also investigated.

Results: The association of propofol and remifentanyl allowed hemodynamic stability, fast emergence and early recovery. BIS values were correlated to target propofol concentrations, but not to remifentanyl concentrations. Neither complications nor awareness cases were reported.

Conclusions: TIVA-TCI with propofol and remifentanyl is safe and can be used even in morbidly obese patients during bilio-intestinal bypass surgery.

PULMONARY COMPLIANCE EVALUATION DURING PROPOFOL-REMIFENTANIL ANAESTHESIA FOR SPINAL SURGERY

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Background and Aims:

Spinal surgery require the prone positioning of the patient. Nevertheless, induction of anaesthesia is performed in supine position and the patient is turned in prone during maintenance of anaesthesia under mechanical ventilation. In the last years, intravenous anaesthesia technique in neurosurgical operating rooms are common use, but data about effects of change from supine to prone positions during intravenous anaesthesia are not yet available. The current study evaluate changes in the thorax-lung compliance(C) of the patients under remifentanil and propofol anaesthesia after the passage from the supine to the prone position for spinal surgery.

Methods:

The study consisted of 15 ASA physical status I and II patients operated for elective spinal surgery. The general anaesthesia was induced with propofol-TCI 2,5-4µg/ml and remifentanil 0,10-0,25µg/Kg/min. Endotracheal intubation was accomplished with cisatracurium(0,2 mg/kg). Respiratory mechanics such as peak inspiratory pressure, plateau airway pressure, pulmonary compliance were recorded using a Drager respiratory device (Julian or Primus) at three time points: after induction of anaesthesia, 10 min after posturing the patient and at the de-curarisation. One way ANOVA was used for analysis of differences in the data before and after turning the patient. For all comparisons $p < 0,05$ was considered significant.

Results:

N. of patients	15
Age	47,6
Compliance	
Supine position	45,4
Compliance	
Prone position	38,2

Conclusions:

Turning patients from supine to prone position during total intravenous anaesthesia reduce significantly the pulmonary compliance.

References:

Tanskanen P. et al. Acta Anesth Scand 1997May;41(5):602-6.

Manna EM et al. Middle East J Anaesthesiol 2005 Oct;18(3):623-30.

ON-LINE PHARMACOKINETIC SIMULATION OF BLOOD AND EFFECT-SITE CONCENTRATIONS OF AN INTRAVENOUS ANAESTHETIC WITH A HARDWARE BOX

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Introduction:

Estimation of blood and effect-site concentrations of an intravenous anaesthetic by pharmacokinetic simulation is a key technology in the practice of intravenous anaesthesia. Generally, the use of a PC and a simulation programme is necessary for such simulation in an operating theatre unless a TCI pump is available. We developed a hardware box, PkBox, for an exclusive use in intravenous anaesthesia. This box receives data on-line from an infusion pump, and displays the concentrations in real-time.

Materials and Methods:

PkBox is a battery-powered compact (H: 9 cm, W: 14 cm, D: 4 cm) equipment with a 16-bit embedded computer board and a liquid crystal character display (LCD). PkBox communicates with an infusion pump via an RS-232C interface, retrieves information on the status of the pump, then calculates blood and effect-site concentrations of an intravenous anaesthetic based on the compartment pharmacokinetic model. The concentrations are displayed on the LCD, and they are updated every five seconds. The latest version of PkBox includes sets of pharmacokinetic parameters for fentanyl, remifentanil, propofol, and vecuronium. Graseby and Terumo pumps are available with PkBox.

Results and Conclusions:

PkBox is tested at authors' institutions. Reliability of concentrations displayed on PkBox was confirmed by a PC-based pharmacokinetic simulation. In clinical practice, on-line pharmacokinetic simulation with PkBox was helpful to anaesthesiologists in adjusting an infusion rate of an intravenous anaesthetic and maintaining an appropriate depth of anaesthesia.

DEXMEDETOMIDINE MAINTAINS BLOOD PRESSURE AT A HIGH LEVEL AFTER INDUCTION AND BLUNTS THE CARDIOVASCULAR RESPONSE TO SKIN INCISION AND STERNOTOMY

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We evaluated an anesthetic-sparing effect of dexmedetomidine (DEX) combined with anesthetics before anesthetic induction on hemodynamics for cardiovascular surgery.

Methods:

Fourteen patients who were scheduled for cardiovascular surgery participated in this study. The patients received an initial dose ($1.0 \mu\text{g}\cdot\text{kg}^{-1}$) of DEX or saline as placebo for 10 min followed by continuous infusion at $0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ until sternotomy before anesthetic induction. Anesthesia was induced and maintained with propofol and fentanyl using a target-controlled-infusion system. The target of effect site concentration (ESC) of fentanyl was set to $4.0 \text{ ng}\cdot\text{ml}^{-1}$ in the placebo group and to $2.0 \text{ ng}\cdot\text{ml}^{-1}$ in the DEX group 5 min before skin incision (SI) and sternotomy (ST). Hemodynamic values (systolic, diastolic blood pressure (SBP, DBP), and heart rate (HR)) were recorded before and after SI and ST. The percent changes due to SI and ST were calculated.

Results:

SBP/DBP in the DEX group before SI were $131\pm 12/63\pm 14\text{mmHg}$ and were significantly higher than those ($86\pm 11/41\pm 6\text{mmHg}$) in the placebo group. The percent increase in SBP in the DEX group during SI was $2.1\pm 2.3\%$ and was significantly lower than that in the placebo group ($31\pm 20\%$). The percent increases in HR in the DEX group during SI and ST ($0.2\pm 0.6\%$ and $2\pm 3\%$) were significantly lower than those in the placebo group ($7\pm 5\%$ and $8\pm 4\%$).

Conclusion:

It is clarified that dexmedetomidine, in addition to its strong anesthetic-sparing effect, kept blood pressure high when combined with anesthetics.

REMIFENTANIL TCI PCA AS A TRANSITION FOLLOWING MAJOR ABDOMINAL SURGERY

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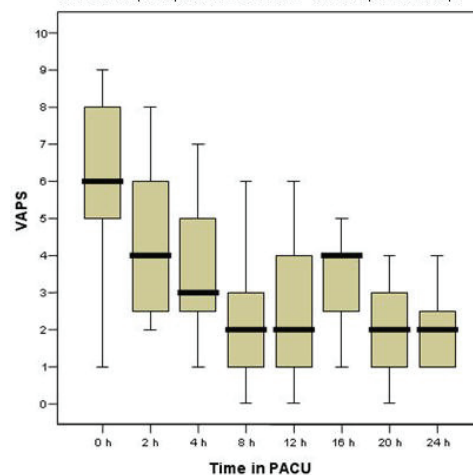
Aim: We report our experience with TCI PCA remifentanyl for the transition from peroperative to postoperative analgesia in 7 patients anaesthetised by propofol/remifentanyl TCI for major abdominal surgery.

Methods: On completion of surgery, remifentanyl effect site concentration (C_e) was reduced until emergence and maintained during transfer to the postanesthesia care unit (PACU). Thereafter, a handset connected to the TCI system was given to the patient who could increase C_e by 0.2 ng/ml every 2 minutes. C_e decreased automatically by 0.2 ng/ml each 30 minutes if no demand was made. No other co-analgesic (paracetamol, NSAIDs, local anaesthetics or morphine) were used. Patients were observed during 24h in the PACU.

Results: Postoperative C_e evolution showed a great interindividual variability (mean range, $0.46\text{--}6.44 \text{ ng/ml}$). Pain scores are presented in figure 1. We had no episode of hypoxemia or respiratory depression requiring staff intervention. Sedation scores were moderate at the arrival but fell rapidly. 4 patients were slightly hypercapnic (maximum $\text{PaCO}_2 = 53 \text{ mmHg}$). One patient necessitated treatment for intense nausea.

Conclusion: In the PACU, remifentanyl effect site PCA could be envisaged as an alternative transition postoperative analgesia technique after major abdominal surgery.

Figure 1. Postoperative pain evaluated by visual analog pain score (VAPS). Figure shows box-plot of median value (bar), 75% and 25% quartile of values (box) and maximum values (whiskers).



HEMODYNAMIC CHANGES CAUSED BY ANTI-TRENDELERBURG POSITION IN TIVA ANESTHETIZED PATIENTS OF DIFFERENT ASA GROUPS

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Introduction: New surgical techniques, bring new challenges for anesthesiologists. Patient's position depends on surgery technique demands, patient's condition and physiological and pathophysiological changes that might be caused by that position.

Aim of Study: Influence of anti-Trendelenburg position on the hemodynamic changes in anesthetized patients in accordance with ASA classification.

Materials and methods: 180 patients were divided into: Group I - 90 patients ASA I/II and group II - 90 patients ASA III/IV). Research consisted of five temporal stages: T1-just before the undergoing into anesthesia; T2-after the undergoing into anesthesia; T3-5 min, T4-15 min and T5-30 min after the setting of the patient into AT position. Monitoring included HF, art. pressure, CVP, PCWP and minute heart volume.

Results: In group I is recorded an increase of HF for 17% as well as a decrease of systolic AP for 20.8%, MAP for 16%, diastolic AP for 19.7%, CVP for 21.2%, PCWP for 23,4% and MV for 19.5%. More significant decrease of hemodynamic monitoring parameters values is found in group II ($p < 0,001$). In this group recovering period of the cardiovascular function, is longer, use of vasopressors or a necessity of setting the patients back into horizontal position, in order to stabilize hemodynamics, more frequent.

Conclusion:

Placing the patient in AT position causes significant hemodynamic changes more frequent in ASA III/IV. Basic factors that affect beginning and intensity of hemodynamic changes are: age, previous cardiovascular state, degree and speed of setting the patient into AT position.

Key Words:

AT position, hemodynamic changes, TIVA

TOTAL INTRAVENOUS INFUSION (TIVA) WAS USED IN RACHILYSIS SURGERY

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Purpose The advantage of total intravenous infusion (TIVA-TCI) was assessed in Rachlysis surgery in the current study Method 32 scoliosis patients were assigned two groups, 17 in TIVA group and 15 in Control. The tracheal intubation was performed by fast induction in two groups, Anesthesia in TIVA group was maintained by TIVA-TCI, which the infusion rate of remifentanyl

and Propofol was accommodated by MAP level. Anesthesia in Control group was done by complexed intravenous-inhalation anesthesia, which the dose of Fentanyl was $5-7\mu\text{g}\cdot\text{Kg}^{-1}$ and concentration of inhalation isoflurane was 1.0-1.5%. For spinal cord protection dexamethasone (5-10 mg) and mannitol ($0.5\text{g}/\text{Kg}^{-1}$) as dehydration were given before rectification procedure. After the procedure waken-up test was done .IBP,CVP,HR,ETCO₂ and SEP were normally monitored. Result When the TCI of remifentanyl $0.12-0.15\mu\text{g}\cdot\text{Kg}^{-1}\cdot\text{min}^{-1}$ and propofol $80-100\mu\text{g}\cdot\text{Kg}^{-1}\cdot\text{min}^{-1}$ in TIVA group, MAP was stable and controlled as 60-65mmHg without using vascular dilator agents. Blood loss was $664\pm 320\text{ml}$, The time of waken-up was 5.6 ± 1.2 min. In group B, IBP was vary greatly and very difficult to control , The MAP controlled by vascular dilator agents was at 60-75mmHg , blood loss was higher than TIVA group ($984\pm 325\text{ml}$, $P < 0.01$), Waken-up time was 10.25 ± 2.5 min. There were no spinal cord injury in two groups. Conclusion TIVA-TCI not only provide desire analgesia , but it also facilitate to control MAP in the rachlysis surgery without using vascular dilator agents. Waken-up test is still golden standard to detect whether spinal cord being injured, TIVA-TCI can shorten the waken-up time.

THE INCIDENCE OF POSTOPERATIVE NAUSEA AND VOMITING FOLLOWING GENERAL ANESTHESIA WITH PROPOFOL OR SEVOFLURANE

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Background:

Volatile anesthetics are a main cause of postoperative nausea and vomiting (PONV). On the other hand, propofol has antiemetic effect. We compared the incidence of PONV after propofol anesthesia with that after sevoflurane anesthesia. Methods: In this study, 172 adult patients scheduled for gynecological or otolaryngologic surgery were enrolled. Our standardized anesthetic technique consisted of propofol for induction, vecuronium and fentanyl for intubation. The maintenance of anesthesia was performed with propofol or sevoflurane without nitrous oxide and fentanyl supplements if required for maintenance of anesthesia. Gynecological patients underwent epidural anesthesia and analgesia during perioperative period. The incidence of PONV was evaluated in the recovery area in the operating theater (RA) for an hour and in the ward on the day of surgery and postoperative day 1.

Results:

There were no significant differences between the groups with respect to demographic data and duration of anesthesia. The incidence of vomiting in RA was significantly lower in the group of patients received propofol compared with the group received sevoflurane. There were no significant differences between groups with nausea in RA and nausea and vomiting in the ward.

Conclusions:

The maintenance of anesthesia with propofol reduces the incidence of vomiting during the early postoperative period compared with sevoflurane.

REMIFENTANIL EFFECT-SITE CONCENTRATION BLUNTING CARDIOVASCULAR RESPONSES TO TRACHEAL INTUBATION FOR DIFFERENT AGE GROUPS DURING PROPOFOL INFUSION

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Background: Tracheal intubation induces clinically adverse hemodynamic changes. Various pharmacological strategies for controlling these responses have been suggested with opioids being widely used. The purpose of this study was to determine the effect site concentration of remifentanyl in blunting the cardiovascular responses to tracheal intubation according to different age groups.

Methods:

Seventy ASA physical status I or II patients, undergoing elective surgery, were classified into Group 1 (age: 12-19yrs, n=25), Group 2 (age: 20-40yrs, n=25) and Group 3 (age: 41-65yrs, n=20). Anesthesia was induced using a propofol target controlled infusion (TCI: Marsh model) with initial concentration of 4 µg/ml. Rocuronium 0.6 mg/kg was administered after the patients lost consciousness. Remifentanyl TCI (Minto model) was started 1 minute after propofol injection. An effect-site concentration of 3 ng/ml was initially chosen. The next concentration was chosen using the up-and-down method reported by Dixon. The non-invasive blood pressure and heart rate were recorded before induction (baseline), after the remifentanyl injection, immediately after intubation as well as 1 and 3 minutes after intubation.

Results:

Remifentanyl effect-site EC50 in group 1 was 1.43 ng/ml, group 2 was 1.82 ng/ml and group 3 was 2.04 ng/ml, respectively. There was no significant difference between the three groups statistically.

Conclusions:

The effect-site concentration of remifentanyl blunting the cardiovascular responses to tracheal intubation during propofol TCI anesthesia did not show significant difference between age groups.

TIVA WITH PROPOFOL FOR URGENT CAESAREAN SECTION

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Namely in the end of year 2000, our hospital had a lack of anesthetic drugs; such circumstances imposed us to put in use Propofol in obstetric anaesthesiology, for UCS.

Key Words: Anaesthesia, Obstetric

Anaesthetic agent: Propofol

Anaesthetic technique: TIVA

Recovery: Maternal awaken

Neonatal: Weight, Apgar score

Materials and Methods: 60 parturients ASA I & II status, at 38-40 gestational week, underwent TIVA for urgent Caesarian Section, caused by different obstetric disorders.

Results: Maternal: Induction, anesthesia, maintenance anesthesia, awaken, recovery time, postanesthetic nausea and vomitus are recorded in PACU. Propofol induction was smooth, without excitation and hiccups; with a slight cardiovascular and minimal respirator depression. Induction time was about 30-60 sec. After giving muscle relaxant, all the patients are successfully intubated. Also recovery from anesthesia is rapid and with minimal adverse side effects (low incidence of nausea and vomiting).

Neonatal: Neonatal weight is variable, 3950 ± 1950. Concerning the placental transfer of Propofol, neonatal Apgar score is accessed on 1st, 5th, 10th minute.

Discussion: Propofol, as a relatively new potent hypnotic agent provides useful anesthetic action depending upon the dose and technique of administration. Its low molecular weight and none dissociative form decrease his placental across. Also, neonatal effects and placental transfer are dose depending as well as the duration of anesthesia pre partum.

Conclusion: In conclusion, our modest study shown none significant differences from other authors and

indicate Propofol's using in obstetric anesthesiology as quality issue and save alternative.

TIVA WITH PROPOFOL FOR URGENT CAESAREAN SECTION

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Propofol, 2,6 disopropylphenol, an emulsion in soya bean oil, founded in 1983 is widely accepted in anesthesiology. In a period of time, 2000 our dept. had lack of anesthetics; this imposed us to use Propofol for UCS.

Key Words: Obstetric Anaesthesia, TIVA, maternal recovery, Apgar score.

Material and Methods: 60 parturients ASA I & II status, at 37-40 gestational week, underwent TIVA for urgent Caesarian Section, caused by different obstetric disorders. As premedication are used benzodiazepins. Propofol inducing dose (2.0-2.2mg/kg) is slowly injected, cold and diluted (avoiding the pain), followed by relaxant. Maintenance of anesthesia was standard: O2:N2O, 50:50 until birth, 30:70 after + Fentanyl + Pancuronium.

Results: Induction was smooth, without excitation and hiccup, minimal cardiovascular and respirator depression; induction time: 30-60sec. Only in 7 patients we have reversible skin reaction. Recovery was fast, first verbal response 4.8 ± 0.7 , without side effects.

Neonatal assesment: immediate cry, neonatal weight 3950 ± 1150 , height 50 ± 3 , Apgar score is shown on table 1.

Min-----Apgar Score-----№ of neonates

1st _____	<6.....	4
_____	6-7.....	33
_____	7-8.....	21
_____	>8.....	6
5th _____	≤8.....	17
_____	>8.....	47
10th _____	≤9.....	25
_____	>9.....	39

Discussion: Propofol provides useful anesthetic action depending upon the dose and technique of administration. Neonatal effects and placenta transfer are dose depending as well as duration of anesthesia prepartum.

Conclusion: In conclusion, our modest study shown none significant differences from other authors and indicate Propofol's using in obstetric anesthesiology as quality issue and save alternative.

TIVA IN THE MAINLY ANALGESIC ANESTHESIA IN NEUROSURGERY: COMPARISON REMIFENTANIL-SUFENTANIL

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Aim:

The aim of our study is to value the possibility of making a mainly analgesic anesthesia using remifentanil and propofol both in continuous infusion and in bolus, trying to establish the real need of analgesic, compared with an anesthesia with sufentanil and propofol.

Materials and Methods:

30 patients who undergo a stabilization of vertebral column were enlisted, and they were divided in two groups. Both groups received premedication with midazolam 5mg/os and atropine 0,01mg/kg. In the first group, ten minutes before induction was administered remifentanil 0,5mcg/kg, followed by a continous infusion by pump of remifentanil at dosage of 0,5 mcg/kg/min and propofol at dosage of 6mg/kg/ h until the end of surgical practice; in the second group, ten minutes before induction was administered sufentanil 15 mcg in bolus, followed by a continous infusion by pump of remifentanil at dosage of 1mcg/kg/h and propofol at dosage of 6mg/kg/h until the end of surgical practice. The infusion of sufentanil was stopped about 50 minutes before the end of surgical intervention in reason of physiologic store of this opioid. In all the patients were monitored continuesly blood pressure, cardiac frequency, SpO2, recording data in the perioperative period. They were registered time of reawakening, of apnoea, of operation, total time of anesthesia, and adverse reactions (nausea, vomit, itch, thoracic rigidity); could be resigned from operative room the patient with Aldrete score ≥ 9 .

Results:

For PAS, PAD, FC, SpO2, the only difference vas the reduction of PAD in the first group, during the greatest painful stimulation period. It's vas registered a significant increase of itch in the second group, and it's

absence in the first group. Nausea was present in 3 patient of the first group and 5 patient of the second group, even if of low intensity. Vomit was present in 2 patients of the first group and 5 of the second group, and it was treated with metoclopramide 10 mg e.v. The time of reawakening was longer in the second group (6.5 min±1.8), than the first group (2,9 min±1.1) In the first group 1 on 15 had apnoea while in the second group 3 patient on 15. There wasn't thoracic rigidity or adverse reactions as bradycardia or hypotension in the two groups. In the first group the propofol titrate was about 4,5mg/kg/h; in the second group was 3,5mg/kg/h. Patients who required analgesic therapy with FANS in the room were 6 in the first group and 5 in the second (VAS 6-10).

Conclusions:

Low dosage of remifentanil by continuous infusion allow the execution of interventions of vertebral column stabilization. Besides the technique of anesthesia mainly analgesic with remifentanil guarantee a greater safety than anesthesia mainly analgesica with sufentanil, for a quick and sure perioperative patient's recovery.

PUPIL DILATION RESPONSE TO NOXIOUS STIMULATION DURING PROPOFOL SEDATION

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The pupil dilates markedly in response to increasing noxious stimulation. however, a central unresolved issue is whether this pupil dilation response (PDR) is a spinal sympathetic reflex or not. Our previous reports indicate that the PDR could be a brain-mediated response such as a defense response, and examined whether the amplitude in PDR, SEP are decreased during propofol sedation (0.3,0.6,0.9µg/ml = 0.3P, 0.6P, 0.9P).

Result:

1. The amplitude of SEP to noxious stimulation during 0.6P, 0.9P significantly decreased compared to that to control.
2. The amplitude of PDR to strong stimulation during 0.9P significantly decreased compared to that to control.
3. The VAS during 0.9P significantly decreased compared to that to control.
4. BIS value were positively related to PDR, SEP and VAS with strong stimulation.

We concluded that PDR to noxious stimulation is an objective parameter for sedation level and a more complex brain response.

